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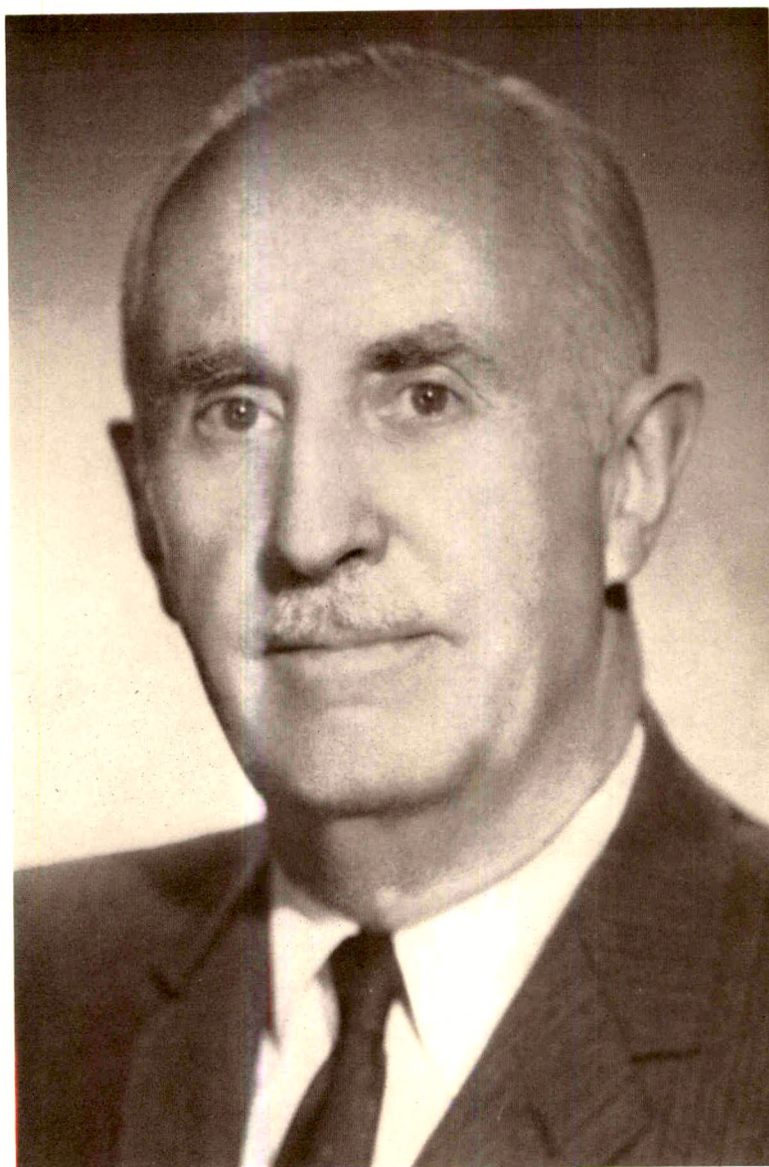
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CONSIDERATIONS IN THE TREATMENT OF RETICULOENDOTHELIOSIS*

THE JANEWAY LECTURE, 1964

By HAROLD W. DARGEON, M.D.

IMPORTANT studies from many clinical^{1,4,6,22,24} and experimental^{11,15,23,25,26,29} sources during the last 2 decades have measurably increased our understanding of some of the remarkable activities of the reticuloendothelial system.^{13,18,21,30} The pathologic states are still acceptably grouped into three general categories, the lipid, the infectious, and the reticuloendothelioses. The genetic factor in the first group, the lipoidoses, which includes Niemann-Pick, Tay-Sachs, and Gaucher's diseases, continues to be reaffirmed and the prognosis is still serious to hopeless. The infectious granulomas, which form the next group, caused by many varieties of microorganisms, including bacteria, fungi, and viruses, are now in many instances amenable to therapy by antibacterial drugs. The third group, known by various terms such as reticulogranuloma, histiocytosis x, and here as reticuloendotheliosis, has been receiving increasing attention for several important reasons. First, there is frequently a great disparity between the clinical and

anatomic manifestations of the disease. Then the variability of the course in different patients may be extreme in spite of identical histologic findings. In some children the process may be only a localized, relatively innocuous condition, while in others the involvement may be widely disseminated, acute, subacute, or chronic in duration, and perhaps incurable by current modalities. Furthermore, the pathology of some of the less differentiated varieties may suggest a malignant neoplastic process. It is evident that attempts to include so many possible syndromes in the categories of eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease will fail and not succeed in embracing all the clinical presentations observed. Confusion, particularly with respect to therapy and prognosis, has resulted from this endeavor. While many authorities^{13,21,22} consider the three members of this group to be different pathologic degrees, namely exudative, proliferative, or fibrotic, of the same process, the clinical manifestations

* Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13-16, 1964.

From the Department of Pediatrics, Memorial Hospital for Cancer and Allied Diseases.

are too diverse to conform to this microscopic classification alone.

MATERIAL AND METHODS

Sixty-two cases of reticuloendothelioses in children were reviewed. One was a New York Hospital case, 5 were from St. Luke's Hospital, and 56 were from Memorial Hospital.

Fifty-two of the cases may be classified, some with reservations, under one of the three following syndromes: (1) solitary

(eosinophilic granuloma); (2) disseminated (Hand-Schüller-Christian syndrome); (3) malignant (Letterer-Siwe syndrome). In addition, there were 10 patients in whom the anatomic findings, the clinical presentation and response to therapy were sufficiently unique to warrant classifying them as "variants." (Table 1).

SOLITARY: EOSINOPHILIC GRANULOMA

There were 24 cases in this group (Table 11).

TABLE I
SUMMARY OF 62 CASES OF RETICULOENDOTHELIOSIS (JUVENILE AGE GROUP)

Variety	No. of Cases	Male	Female	Age (yr.)	No. of Cases	Status
Solitary (eosinophilic granuloma)	24	13	11*	<2	6	L: NED**
				3	4	1-4 yr.: 5
				4	3	5-10 yr.: 10
				5-13	11	10+ yr.: 5 (4 lost to follow-up)
Disseminated (Hand-Schüller-Christian syndrome)	18	13	5	<2	10	L: NED
				3-4	8	5-9 yr.: 1
						10+ yr.: 6 (2 have diabetes insipidus)
						L: D. Active
Malignant (Letterer-Siwe syndrome)	10	7	3	<2	7	1-4 yr.: 6
				3	3	10+ yr.: 1
						Died
						3 yr. A.O.: medulloblastoma
Variants	10	6	4**	<4	9	14 yr. A.O.: xanthomatosis, astrocytoma
				11	1	Died
						3 yr. A.O.: 7
						1-2 yr. A.O.: 3
						L: NED
						1-15 yr. A.O.: 5
						L: D. Active
						2 and 10 yr. A.O.: 2
						Died
						1 yr. A.O.: 3

* Two Orientals, ** 1 Negro.

L:NED=Living, no evidence of disease.

L:D. Active=Living, disease active.

[A.O.=After onset.

TABLE II
SUMMARY OF SOLITARY CASES (EOSINOPHILIC GRANULOMA)
13 Males—11 Females,* Total: 24

Age (yr.)	No. of Cases	Status
<2	6	1-4 yr. (5)
3	4	5-10 yr. (10)
4	3	10+ yr. (5)—4 lost to follow-up
5-13	11	

* Two Orientals.

L:NED=Living, no evidence of disease.

Age and Sex. Thirteen were under 5 years of age. There were 13 boys and 11 girls.

Symptoms. Twenty-three of the 24 patients were in pain, an important symptom of many serious bone diseases in the young. Swelling and tenderness at the site of the lesion were present in almost two-thirds of the cases.

Sites. Various bones were involved, but more flat bones (15) than tubular (11) were affected. Only 2 patients had skull lesions. One of these 2 also had disease in a rib, the other in the left radius.

Diagnosis. The difficulties in roentgenographic diagnosis were confirmed by the reports forwarded from referring physicians

and various institutions. There were only 10 correct original diagnoses, 5 were equivocal or doubtful and 9, *i.e.*, more than one-third, were diagnosed as a malignant tumor or as an infection.

Treatment. In 22 of the 24 children, treatment was instituted promptly—less than 8 weeks from apparent onset. The measures used were: biopsy alone in 2 cases and surgery alone in 5 cases. Biopsy or surgery with chemotherapy was used in 4 cases and biopsy or surgery with irradiation in 13 cases.

Status. Twenty patients are living with no evidence of disease. Five are living more than 10 years, 1 of whom is living 33 years

TABLE III
SUMMARY OF DISSEMINATED CASES (HAND-SCHÜLLER-CHRISTIAN SYNDROME)
13 Males—5 Females, Total: 18

Age (yr.)	No. of Cases	Status
<2	10	L: NED 5-9 yr. (1) 10+ yr. (6) 2 have diabetes insipidus
3-4	8	L: D. Active 1-4 yr. (6) 10+ yr. (1) Died 3 yr. A.O. medulloblastoma *14 yr. A.O. xanthomatosis-astrocytoma * 2 yr. A.O. * 1 yr. A.O.

* Elsewhere.

L:NED=Living, no evidence of disease.

L:D Active=Living, disease active.

A.O.=After onset.

from onset; 10 are living 5 to 9 years after onset and 5 are living 1 to 4 years after onset. Four were lost to follow-up.

DISSEMINATED RETICULOENDOTHELIOSIS:
HAND-SCHÜLLER-CHRISTIAN SYNDROME

There were 18 patients in this group (Table III).

Age and Sex. All were 4 years old or less; 10 were under 2 years of age. There were 13 boys and 5 girls.

Symptoms. Pain was present in only 10 instances, but swellings occurred in 13 patients.

Diagnosis. Roentgenographic diagnosis was correct in 17 of the 18 patients. The skull was involved in 16 patients; the characteristic calvarial defects simplified the diagnosis. The total number of bones involved ranged from 3 to 8. Only 2 patients had the so-called classic triad of the Hand-Schüller-Christian syndrome, including proptosis, osteolytic calvarial defects, and diabetes insipidus.

Treatment. This was not promptly instituted; only 4 children received therapy less than 8 weeks from onset; 5 were sick 3 to 9 months before receiving treatment, and 9 had symptoms from 1 to 3 years prior to therapy. Five patients were treated by irradiation following biopsy. Four children had surgical curettage, irradiation and chemotherapy. Eight patients were treated by biopsy, irradiation, and chemotherapy, and 1 patient was treated by biopsy and chemotherapy.

Status. Fourteen patients are living, 7 of whom are living 5 to 15 years with no evidence of disease. Of the remaining 7 living patients, 6 are living 1 to 3 years with active disease and 1 is living 16 years with active

though indolent disease. Two of the children have diabetes insipidus controlled by pitressin insufflations.

Of the 4 patients who have died, 1 had central nervous system xanthomatosis and an astrocytoma. This child survived 14 years after onset. Another patient who died had a medulloblastoma. This boy received 7,880 r to the head and neck at another institution from his fourteenth to forty-second month of age. Data on the 2 other children, who expired elsewhere, are not available.

MALIGNANT: LETTERER-SIWE SYNDROME

In this group there were 10 children (Table IV).

Age and Sex. All were under 5 years of age. There were 7 boys and 3 girls.

Symptoms. The clinical presentation and course of the disease were quite different from those of the previously described syndromes. Nine children had histories of persistent illness, often from birth, including otitis media, stomatitis, recurrent respiratory infection, and refractory seborrhea or eczema. All 10 had significant enlargement of the liver or spleen, or both. Five showed skeletal disease on roentgenographic examination. One child showed healing lesions of the skull despite a declining fatal course. Nine children were anemic and 3 had thrombocytopenic purpura. Two of a total of 6 bone marrow examinations were normal; 1 suggested monocytic leukemia, 2 showed a significant increase in reticulum cells and 1 demonstrated many neoplastic cells believed to be of the reticulum-cell type.

Treatment. Four patients received irradi-

TABLE IV
SUMMARY OF MALIGNANT CASES (LETTERER-SIWE SYNDROME)
7 Males—3 Females, Total: 10

Age (yr.)	No. of Cases	Status
<2	7	Died <1 yr. after onset (7) 1-2 yr. after onset (3)
3	3	

TABLE V
SUMMARY OF "VARIANTS"

Age (yr.)	No. of Cases		
<1	5		
2	2	Males	6
3	2	Females	4
11	1		Total: 10

Symptoms
swelling—7, lymphadenopathy—6, liver enlargement—6, spleen enlargement—4, fever—5, pain—5, rash—5, infection—5, anemia—4, triad*—2, obesity—1, heart (congenital)—1, dislocated hip—1

Skeletal involvement
multiple—6, skull only—1

Therapy

Surgery	Roentgen Therapy	Chemotherapy	Status
+	+	+	3 living—15, 6, 2, yr. after onset 1 dead—1 yr. after onset
o	+	+	2 living—10, 9 yr. after onset 1 dead—1 yr. after onset
o	o	+	2 living—6, 1 yr. after onset
+	+	o	1 dead—1 yr. after onset

* Triad: proptosis, calvarial osteolytic defects, diabetes insipidus.

ation to osseous lesions, 1 patient with thrombocytopenic purpura had a splenectomy, and all received various chemotherapeutic agents, including: steroids, 6; nitrogen mustard, 3; methotrexate, 4; and purinethol, 3. All died less than 2 years after onset, 7 patients in less than 1 year. Four had necropsies with the following findings: two had malignant reticuloendotheliosis, 1 had malignant reticuloendotheliosis or reticulum cell sarcoma, and another had Hand-Schüller-Christian disease with multiple lesions.

VARIANTS

Ten patients, 6 boys and 4 girls, all except 1 under 4 years of age (5 were less than 6 months old, 4 were aged from 24 to 36 months, and 1 was 11 years of age), had several unusual features and are therefore classified as variants (Table v).

Symptoms. The onset usually was acute but no consistency was noted otherwise in the initial presentations.

Diagnosis. Lymphadenopathy was present in 6 patients; pain, infections, fever and rash occurred in 5 children, and anemia in 4. The liver was enlarged in 6, the spleen in 4 patients. One marrow examination showed a moderate eosinophilia, while in 7 others marrow studies were normal. The Hand-Schüller-Christian triad was present in 2 patients. Skeletal involvement occurred in 7.

Treatment. Treatment was instituted within 8 weeks in all 10 cases. There are seven survivors without evidence of disease 1 to 15 years after onset. Four of these according to some pathologists had malignant reticuloendotheliosis. Three survivors received surgery, irradiation, and chemotherapy, 2 had biopsy, irradiation and chemotherapy, and 2 biopsy and chemotherapy.

Of the 3 patients who expired, 1 died of disseminated reticuloendotheliosis; this child had been treated by surgery and irradiation. Another, who also gave evidence



FIG. 1. M. D. October 3, 1956. Osteolytic effect of left frontal bone in a boy aged 16 months. Histologic diagnosis was Letterer-Siwe disease. Treated by roentgen radiation, 500 r, and chemotherapy (6-mercaptopurine, 25 mg. daily for 4 months, then intermittently for 6 months).

of disseminated reticuloendotheliosis, received surgery, irradiation, and chemotherapy. The third patient who died, aged 11 years, had malignant reticuloendotheliosis and received, following biopsy, irradiation and chemotherapy.

COMMENT

A summary of the foregoing data regarding the 62 cases of reticuloendotheliosis is given in Table 1. The slight male preponderance, 39 boys to 23 girls may be due to the limited number of patients in this series. There was 1 Negro, 2 children were Orientals and all others were white. Fifty of the 62 children were under 5 years of age, 28 of whom were less than 2 years old. Among the 38 patients in the disseminated, malignant, and variant groups, there was only 1 child over 5 years of age, a boy of 11 years, whose diagnosis was Letterer-Siwe disease. Hence, there is some clinical support for the prognostic assumption that if

the child is 5 years of age or older and his lesion is solitary, the probability that he has or will have disseminated disease is remote. The prognosis, irrespective of the histology, is therefore guarded to good in such a circumstance. On the other hand, in the younger age groups, even when an initial solitary site is the only detectable finding, further dissemination may occur, and the prognosis must be guarded even if histologically the granuloma is benign.

In Lahey's²⁰ series of 69 patients, excluding the solitary or eosinophilic granuloma variety, there was also a slight male preponderance, a 38 to 29 ratio. Fifty per cent of the children in this series died when affected in the first 3 years of life.

We have observed examples of the disparity between the course of the illness and the pathology of the lesion. One instance, previously reported²⁸ was that of a girl, aged 4 years, with multiple cutaneous, nodular lesions, which were diagnosed histologically as Letterer-Siwe disease. She was treated sporadically with methotrexate. She is now 17 years of age and reports by mail that she is in good health. Another instance was that of a male infant aged 16 months who had a single osseous lesion in the left frontal bone, also diagnosed histologically as Letterer-Siwe disease. He was treated by irradiation and chemotherapy and has had no recurrence in 7 years (Fig. 1 and 2).

DISCUSSION

The therapeutic regimen in diseases that vary so widely in their clinical courses can only be established after appraisal of several factors. The information gained from the history and physical examination is often significant. This includes the age of the patient, the duration of the disease, its effects on his health, the site or sites, as well as the degree of involvement. Roentgenographic aid is valuable, but confusion with bone cyst, tuberculosis, osteomyelitis, and bone sarcomas occurs not infrequently. Scrapings from skin lesions may show histiocytes. Biopsy is mandatory before any

treatment by surgery, irradiation, or chemotherapy is instituted.

It is well known that unicentric bone lesions usually respond satisfactorily to surgical curettage or roentgen therapy. Unfortunately, this is not always the case. If the disease shows multiple foci, the risk of these procedures must be equated with the anticipated benefits. I have observed recurrence in well performed mastoidectomies. Case 6 in Table VI illustrates the ineffectiveness of usually adequate radiation therapy.

Consideration of the use of systemic chemical agents arose in 1947, when a very sick infant, aged 7 months, was referred to St. Luke's Hospital. This girl, reported previously,^{8,9} became ill following a small-pox vaccination which had been performed at 6 months of age. The cases of Sewall,²⁷ of Delano and Butler,¹⁰ of Elliott,¹² and of Cochran *et al.*⁷ demonstrate that this procedure occasionally may produce serious osseous lesions.

Our patient (Fig. 3 and 4) was operated for an eosinophilic granuloma of the skull, following which she received 500 r to one skull field and 200 r subsequently to the left orbit. At 1 year of age, because of the wide dissemination of her disease (Fig. 5), she was given nitrogen mustard initially and later the antimetabolites, first aminopterin, then amethopterin (methotrexate), in cycles over a period of 9 years (Fig. 6). She is now 17 years old, obese, and has had diabetes insipidus for 15 years, controlled by pitressin; otherwise she is in good health. Sections of the skull tumor and a lymph node have been diagnosed by pathologists of equal competence as eosinophilic granuloma and Letterer-Siwe disease. The satisfactory results obtained by chemotherapy in this infant have now been duplicated sufficiently often, although by no means constantly, to indicate the value of these drugs in many cases. The corticosteroids³ and the antimetabolite purinethol have also shown demonstrable beneficial effects.

The mechanism of the therapeutic action of these drugs is not understood, but, in addition to the disturbances produced by

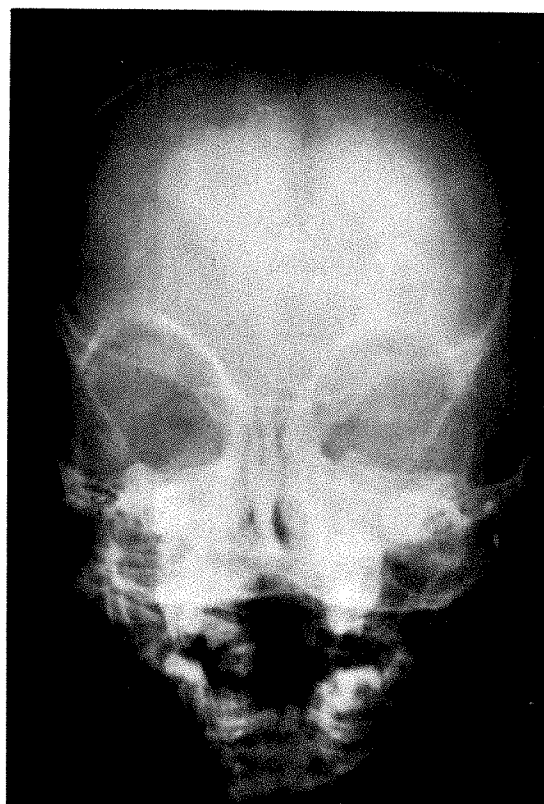


FIG. 2. M. D. March 2, 1957. Lesion healed. No recurrence up to 1963.

most of these agents in the growth of rapidly proliferating cells, the alterations in immune reactions to which reticuloendothelial cells are so intimately related perhaps are of importance.

A further development of major interest to those who believe that many of these syndromes are of infectious origin has been the use of many antibacterial drugs, including isoniazid. It is appropriate here to quote in part Hand's opinions with respect to the etiology of the disease and the value of drugs in treating his patient: "... the thought occurs that the infective agent may gain entrance ... and may be animal (ameboid) rather than vegetable in nature. This theory also offers an explanation for the apparent benefit in my first case following the use of quinine."^{16,17}

There are 4 cases reported in the literature with a diagnosis of Letterer-Siwe disease in which the seriously ill children re-

TABLE VI
CHEMOTHERAPY IN MALIGNANT RETICULOENDOTHELIOSIS

Case Author Year	Race	Sex	Age (yr).		Rash	Clinical Signs				Pathology	Therapy	Comment	Result
			Onset	Admitted		Liver (cm.)	Spleen (cm.)	Lymphad- enopathy	Bones				
1 V.D. Aranson ² 1951	W	F	1½	1½	Petechiae	3.0	1.0	Cv. + Ing. +	Normal	Spleen: Letterer-Siwe disease	1. Splenectomy for thrombo- penic purpura 2. Streptomycin—5 wk.	First histology: "Sarcoido- sis"—postoperatively: con- tinued lymphadenopathy, purpura	NED 14 mo. later
2 (Pe) Bierman <i>et al.</i> ³ 1952	W	M	½	½	+	3.0	1.0	+++	Skull, pelvis, ribs	Lymph node skull disease	1. Penicillin, chloromycetin— 1 mo. 2. Roentgen therapy of skull 3. Dihydrostreptomycin and penicillin, chloromycetin, aureomycin—2 mo.	Some improvement on Rx #1 Relapse during Rx #2 Marked improvement on Rx #3	NED 15 mo. later
3 (Pa) Bierman <i>et al.</i> ³ 1952	W	M	½	½	o	?	?	+++	Skull, pelvis, ribs	Lymph node skull disease	1. Penicillin—1 mo. 2. Aureomycin—10 da. 3. Penicillin, aureomycin, chloromycetin—5 + wk.	No response to Rx #1 Improvement on Rx #2 Marked improvement on Rx #3	NED 23 mo. later
4 Fischer ¹⁴ 1953	N	M	1½	2	o	o	o	Cv. +	Skull and 8 others	Bones: Letterer-Siwe disease <i>B. paracolon Arizona</i> from 2 biopsies and blood	1. Penicillin, chloromycetin— 3 wk. 2. Streptomycin—9 wk. 3. Terramycin—2 mo. Chloromycetin—4 mo. "Spray" Roentgen therapy 200 r air	Progressive disease on Rx #1 and #2. Subsidence on Rx #3	NED 6 mo. later Valgus, left knee
5 K.R. Dargeon 1964	N	F	Birth	#1-Birth #2-6 wk.	++•	6.0+	5+	Generally severe	Pathologic dislocation of left hip	Skin, lymph node: Letterer-Siwe disease Skin, left hip: <i>Staphylo- coccus aureus</i>	1st admission: Penicillin, di- hydrostreptomycin—9 da. 2nd admission: Penicillin, streptomycin—3 da., predni- sone, actinomycin, erythro- mycin—3 wk., surgery left hip	Mother had "arrested" tu- berculosis Herpes 1st trimester Rheumatoid arthritis 3rd trimester	Age 8 yr. NED 6 yr. (hip de- formity)
6 T.B.III Dargeon 1964	W	M	2	3	o	3.0	o	Cv. + +	Skull including left mastoid and 6 others	Lymph node, left fe- mur: Eosinophilic granuloma "shading" to Letterer-Siwe disease	1. Roentgen therapy (11 sites) + antibiotics + TEM, local hospital 2. Streptomycin, nitrogen mustard 3. Roentgen therapy (3 sites), methotrexate 4. Isopriazid—2 yr. + purine- thiol—6 yr. (cyclic)	Progressive disease on Rx #1 Brief, marked improvement on Rx #2. Slowly progres- sive disease on Rx #3. Sub- sidence, complete on Rx #4	Age 11 yr. NED 2 yr. No sequelae

* Severe pitted desquamation, erythema of face, thorax, arms, soles.
NED=no evidence of disease.
Cv.=cervical; Ing.=inguinal

sponded well to therapy with antibacterial agents.^{2,5,14} One of them had a *B. paracolon* isolated from several lesions. We have observed 2 other patients, both seriously ill, improve after the use of antibacterial compounds (Table VI). Their records follow.

ILLUSTRATIVE CASES

CASE 5 (Table VI). K. R.

FIRST ADMISSION. The patient was born in New York Hospital on August 15, 1955, 5 weeks prematurely. She was the fourth living child of a 31 year old Negro mother, who had 1 miscarriage. The mother, who developed tuberculosis in 1951, was still under regular medical observation, and the tuberculosis at the time of this pregnancy was considered arrested; her sputum and gastric washings were negative 1 month prior to delivery. She also had rheumatoid arthritis, one mild attack of which occurred in her third trimester. She was allergic to gold, butazolidin, penicillin, and codeine; none of these drugs was administered during this pregnancy. In the first trimester she had an attack of herpes zoster. The membranes ruptured on August 14, and the baby was born

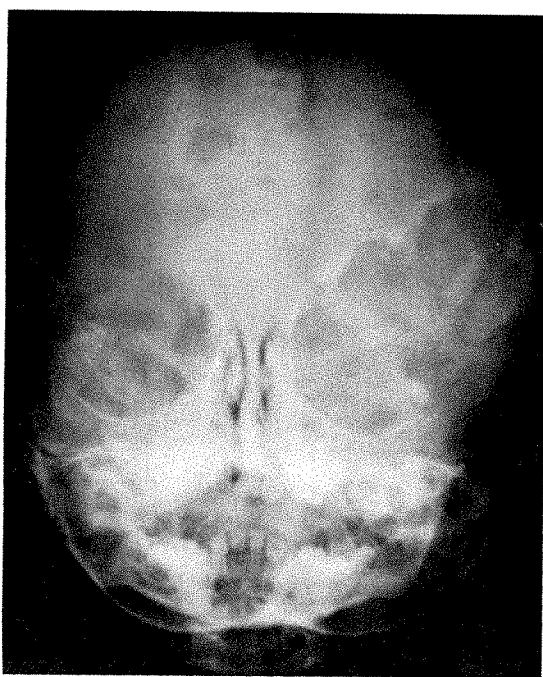


FIG. 3. L. W. July 12, 1948. Skull shortly before chemotherapy was begun. Many typical osteolytic lesions are present.

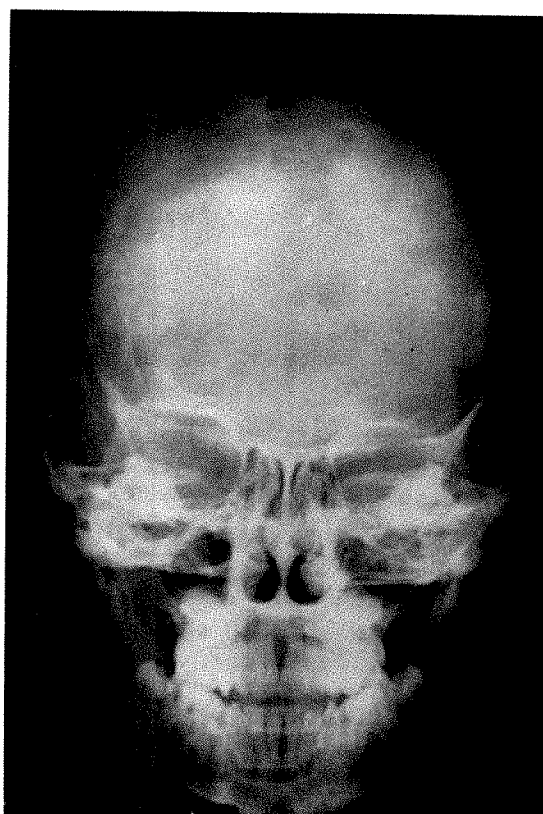


FIG. 4. L. W. October 6, 1950. Only slight suggestions of osteolytic defects remain.

after a 7 hour uncomplicated labor. The amniotic fluid was noted to be greenish.

Physical Examination. The infant weighed 2,460 gm. The circumference of the head measured 29.5 cm., the chest 27.0 cm., and her height was 47.0 cm. She was alert and vigorous. A disfiguring rash about the face was erythematous, serpiginous, atrophic and puckered in many places (Fig. 7). Telangiectasia and petechiae were present. The liver edge and the spleen were both palpable 4 cm. below the costal margins.

Laboratory Findings. The hemogram and urinalysis were normal. The Mazzini, Wassermann and Mantoux (1-10,000) tests were negative. Roentgenograms of the skull and chest were normal. The bleeding time was 8 minutes and the clotting time under 5 minutes.

Course. The infant was placed in an isolette. Neomycin ointment was used on her face. Her feedings were well taken. Penicillin (75,000 units) and streptomycin (75.0 mg.) were given daily over a 9 day period. A mild jaundice, beginning 36 hours after birth and accompanied

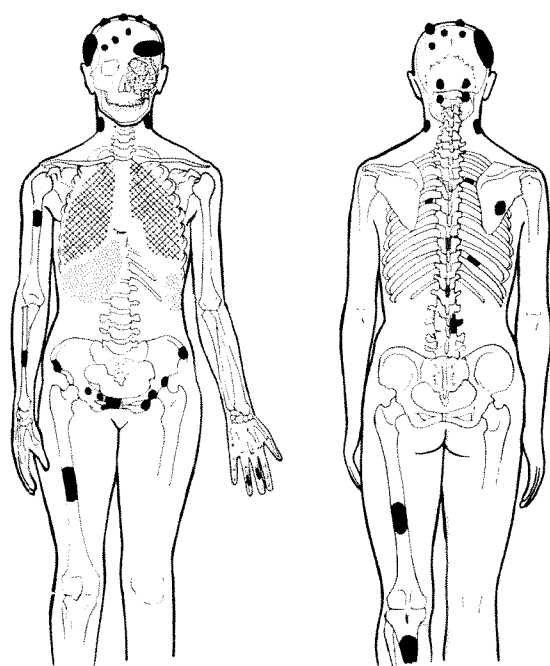


FIG. 5. L. W. Diagram showing sites of lesions observed over a 9 year period. In addition to the skull defects, she had occipital, cervical, and inguinal lymphadenopathy, bilateral pulmonary infiltrations and lesions in 15 other bones. Some of the latter completely healed, while others concurrently developed during these 9 years.

by a fall in hemoglobin to 10.5 gm. per cent, subsided in 5 days. Complement fixation studies for herpes virus demonstrated no antibody. The lesions diminished in size and severity and the infant, weighing 2,340 gm., was discharged and referred to the Out-Patient Department on August 30, 1955.

SECOND ADMISSION. The patient was admitted to the hospital the second time on September 24, 1955. One week prior to admission the rash became more acute and blood appeared in the stool.

Physical Examination. The infant at 6 weeks of age weighed 2,900 gm. and appeared chronically ill. The erythematous, pitted rash involved the scalp, the face, the neck, the thoracic wall, and part of the abdominal wall. Moderate generalized lymphadenopathy was present; the liver was 6 cm. and the spleen 5 cm. below the costal margins.

Laboratory Findings. The urine was normal, the hemoglobin 5.5 gm. per cent, the white blood cell count was 10,200, the differential count was normal and the platelet count was 30,000 per mm.³. The sedimentation rate was 45 mm. in 1 hour; the cephalin flocculation was 7; the thymol turbidity 9 units. The electrolytes, the total protein, the A/G ratio, and prothrombin were normal. Skeletal roentgeno-

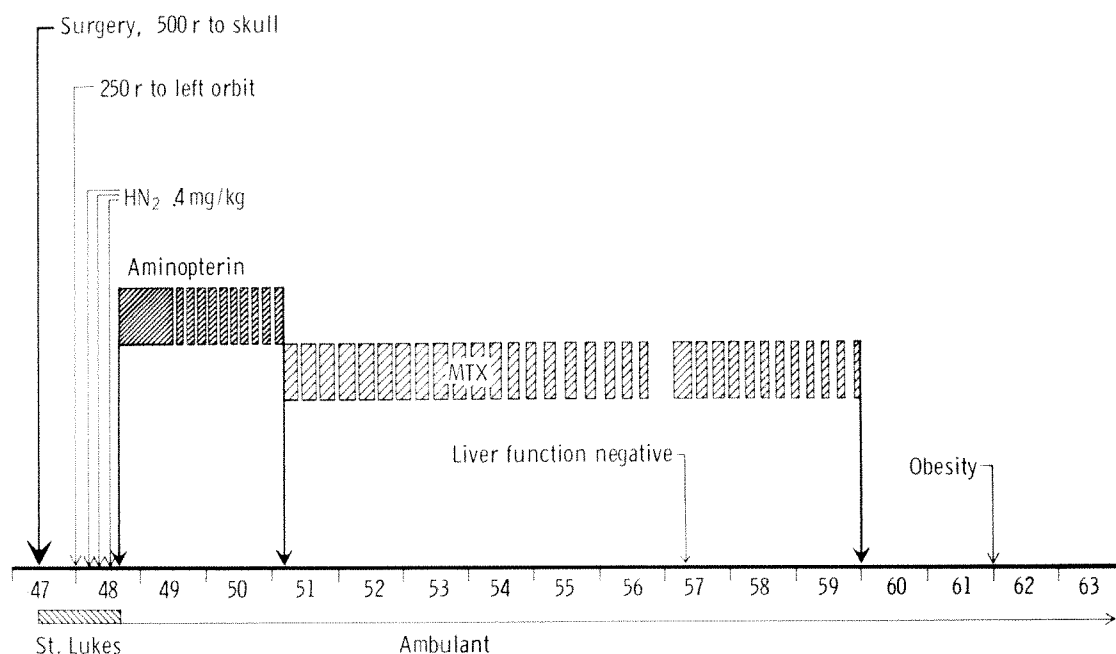


FIG. 6. L. W. Diagram showing therapeutic regimen from 1947-1959. HN₂ = nitrogen mustard, MTX = methotrexate. Roentgen radiation is expressed as air dosage. The divided bars indicate "cyclic" or "intermittent" chemotherapy.

grams showed a dislocation of the left hip.

Course. The infant received multiple transfusions. The bloody stools were attributed to moniliasis and ceased within a few days. *Staphylococcus aureus* was obtained from abscesses of the scalp and buttock that developed later. *Streptococcus hemolyticus* and *E. coli* were also grown from lesions of the latter site. One blood culture grew out *Staphylococcus aureus*. Biopsies of skin and lymph node performed on September 28 were diagnosed as Letterer-Siwe disease. Penicillin (up to 1,200,000 units) and streptomycin (up to 200 mg.) were given daily from September 29 to October 4. This treatment was accompanied by an improvement in the patient's condition.

Following the pathology report, therapy was changed to erythromycin (400 mg.) and achromycin (200 mg.) daily from October 19 to November 8. These drugs were discontinued on November 9, because it was felt that the improvement in her condition was not due to their effects. A relapse occurred after a total dose of less than 30 mg. of meticorten for thrombopenia was given between November 21 and 24. The patient's condition gradually improved and she was discharged to the Out-Patient Department on December 18, 1955, weighing 5,200 gm. In February, 1956, a closed reduction of the pathologic dislocation of the left hip was performed at the Hospital for Special Surgery. Subsequently, in November, 1956, an open reduction was done. Her health during the next 6 years was good. In September, 1963, the left leg was 2.5 cm. shorter than the right, and there was some scarring of the skin at the sites of her previous operations.

In 1957, the mother again became pregnant. In the second trimester her gastric washings showed *M. tuberculosis*. She was hospitalized and given isoniazid and para-aminosalicylic acid; while under treatment she gave birth to a full-term female infant weighing 3,740 gm. This baby had an erythematous rash with atrophic areas on the chest, axillae and perineum. Her Mantoux test (1-1,000) was negative. Skin and lymph node biopsies showed only chronic inflammation. Since then, her health has been good. In May, 1963 she was considered to be a well child.

CASE 6 (Table VI). T.J.B. III. This 3 year old white male was admitted to Memorial Hospital on October 28, 1955.

Present Illness. The boy was in good health until October, 1954, when he complained of left



FIG. 7. Case 5, K. R. Extensive disfiguring rash of face during neonatal period. Histologic diagnosis was Letterer-Siwe disease.

knee and later bilateral leg pains. Roentgenograms taken November 30, 1954, revealed bilateral femoral lesions and also lesions of the skull. Biopsy was taken and the diagnosis of eosinophilic granuloma was made. He was admitted to his local hospital from November 30 to December 12, 1954 and treated with roentgen irradiation of the skull and femurs. During this hospitalization, blood cultures were positive for *Staphylococcus albus*, and he was treated with ilotycin and aureomycin for 2 weeks. At the end of December, a new skull lesion was found and 2 weeks later still another skull defect appeared; both were treated with roentgen irradiation. The boy was readmitted to the same hospital on February 2, 1955 because of enlarged cervical lymph nodes, which were biopsied and revealed evidence of eosinophilic granuloma "... that in some ways ... is beginning to shade over into the Letterer-Siwe pattern."* He was treated with ilotycin and aureomycin. In March, 1955 more cervical swelling was found and the patient was treated with chloromycetin for 10 weeks. From April to September, 1955 new lesions developed in the

* Armed Forces Institute of Pathology #697472.



FIG. 8. Case 6, T. B. III. November 30, 1954. Osteolytic and periosteal lesions in femoral shafts.

left femur, left ilium, right ilium, and skull; each was treated with roentgen irradiation. In September he received a 3 week course of triethylene melamine (0.5 to 3.0 mg. daily). Following this and during the 3 weeks prior to his admission to Memorial Hospital, the patient had further cervical swelling, low grade fever (100–101°F.) and increased irritability. No anorexia, vomiting, weight loss, weakness or fatigue was observed.

Past, Family, Social History. Not contributory.

Physical Examination. The patient's pulse was 114, respiration 24, and temperature 100.6°F. He was a well-developed, well-nourished white male in no acute distress. Skin was negative. His head was normocephalic, with a 2×3 cm. epilated area, clear-cut, over the right parietal region. The ear, nose and throat examination was negative. The neck was supple. There were firm, movable, slightly tender, matted cervical lymph nodes, a 2.5 cm. in diameter raised mass at the left auricular region, a 3.0–4.0 cm. raised mass in the left submandibular region and a 1.5 cm. postcervical lymph node on the left. There were several 1.5 to 2.0 cm. lymph nodes on the right side in the cervical chain. There were palpable small posterior occipital lymph nodes, but no en-

larged axillary or epitrochlear lymph nodes. There were 1.0 cm. movable, slightly hard, slightly tender right inguinal lymph nodes. The lungs were normal. The heart was not enlarged and there were no murmurs. The abdomen was soft and the liver palpable to 3.0 cm. below the costal margin. The spleen and kidneys were not felt. The extremities were negative.

Laboratory Data. Admission hemogram showed a hemoglobin of 10.6 gm. per cent, a white blood cell count of 4,100 with a normal differential, and a platelet count of 380,000 per mm.³. The follow-up hemogram showed the hemoglobin ranging from 10.1 to 10.7 gm. per cent, and a white blood cell count ranging from 2,100 to 7,300. The urinalysis was within normal limits except for a trace of sugar on November 1, 1955. The Mazzini test was negative. Urine culture on October 29 was negative. Nose and throat cultures of October 26 were as follows: *Clostridium welchii*, *Staphylococcus albus*, *E. coli*-aerogenes group, *Neisseria* group and alpha *Streptococcus hemolyticus*. A blood culture on October 28 was negative.

Roentgen Findings. Several osteolytic lesions characteristic of reticuloendotheliosis were present in the calvarium, the left mastoid, the right scapula and both ilia. The shafts of the femurs showed marked osteolytic and productive changes throughout their extent (Fig. 8 and 9). The right humerus, the right radius and the left fifth rib also showed changes consistent with

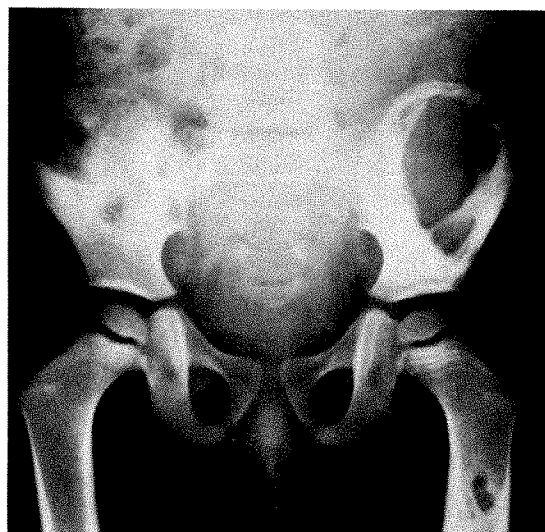


FIG. 9. Case 6, T. B. III. February 27, 1956. Lesions in both ilia and femurs.

the diagnosis of reticuloendotheliosis. The lungs were normal.

Hospital Course. Because of a slight elevation of temperature on admission and marked cervical lymphadenopathy representing a possible adenitis, the patient was placed on a daily dose of penicillin (1,200,000 units) and streptomycin (600 mg.). Within 5 days of this regimen, the cervical lymphadenopathy definitely decreased and he was afebrile. On the seventh day he was given a dose of nitrogen mustard (0.2 mg./kg.). This was repeated on the eleventh day. It was noted that the lymphadenopathy underwent further regression. On the twelfth day he was started on methotrexate 2.5 mg. orally a day. Streptomycin therapy was continued throughout his hospital stay. He was discharged on the fourteenth hospital day to continue with the methotrexate.

Subsequent Course. For the next 6 months he was continued on methotrexate without significant improvement. On August 21, 1956 this drug was discontinued and purinethol (25 mg.) and isoniazid (75 mg.) daily were substituted. He received roentgen therapy (600 r) in August, 1956 for a painful lesion of his right humerus and again in November, 1956 to his left temporal region (600 r), where a draining sinus had persisted for 5 months. During 1957 and 1958 he improved greatly (Fig. 10). In August, 1958 reduction in the dose of isoniazid was begun and in June, 1959 it was discontinued. Reduction in the dose of purinethol was then begun and in May, 1962 this drug was discontinued (Fig. 11). Interval roentgenograms had shown improvement in all osseous lesions and complete healing of some (Fig. 12 and 13).

At no time did he have symptoms of diabetes insipidus or proptosis despite the chronicity of the disease. In 1964 at the age of 12 years he weighed 87 pounds, was 4 feet, 10 inches in height and was considered in excellent physical condition.

Another child, a patient of Dr. William Klingberg,¹⁹ had histologic findings of diffuse reticuloendothelial proliferation. An atypical acid fast organism was obtained on culture of a biopsied site. The child improved while on isoniazid. It is recognized that these few cases do not factually establish a microorganism or its products as an etiologic agent. The clinician, however, is obligated to utilize, often empirically, all

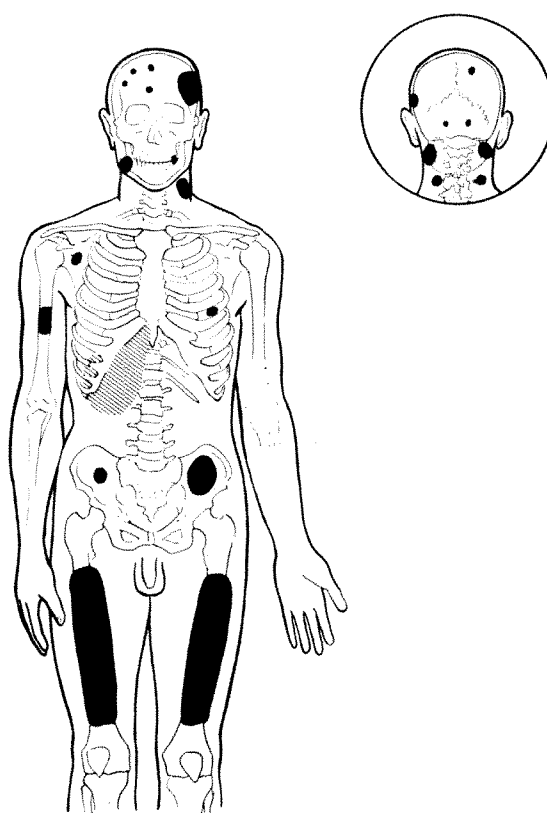


FIG. 10. Case 6, T. B. III. Diagram showing sites of lesions observed during a 6 year period.

means available to aid the patient, even in the absence of a scientifically proved etiology.

THERAPY

Treatment by conventional therapy, surgery and roentgen irradiation, is usually adequate for the solitary cases. However, particularly in the younger child, the subsequent course often cannot be anticipated. The desirability of adjuvant "prophylactic" chemotherapy for a period of 6 months should be considered. In those patients whose disease is not localized, chemotherapy is of primary importance. Surgery and roentgen irradiation may also be required in some circumstances. A suggested plan of approach is indicated in Table VII, subject, of course, to modifications the individual case may require.

The chemical agents in use by us are ni-

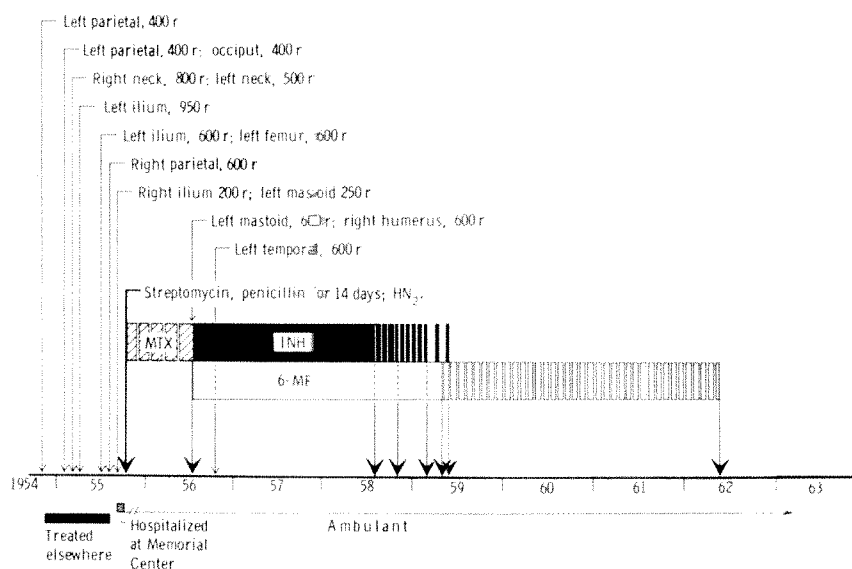


FIG. 11. Case 6, T.B. III. Diagram showing therapeutic regimen, November, 1954 to May, 1962. Roentgen radiation is expressed as air dosage. MTX = methotrexate, INH = isoniazid, 6-MP = 6-mercaptopurine and purinethol. The divided bars indicate "cyclic" or "intermittent" chemotherapy.

trogen mustard (0.2 mg. to 0.4 mg./kg. of body weight intravenously), usually given only once; then methotrexate (0.25 to 2.5 mg. daily) or purinethol (12.5 to 50 mg. daily, depending on the size of the child) is given, both orally. This program is fol-

lowed for 4 to 6 months, sometimes even longer. If improvement occurs, the drug is given on a cyclic basis—3 weeks on, 1 week off, and gradually reduced over a period of months or years to complete cessation. Prednisone and related steroids are of considerable value in some cases but because of side effects cannot be maintained in full dosage for extended periods. The limited experience with antibacterial agents, including antituberculous drugs, places these

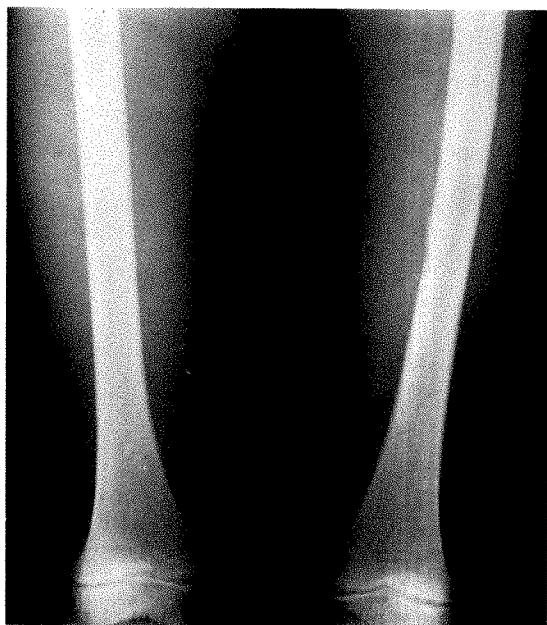


FIG. 12. Case 6, T. B. III. August 28, 1959. Complete healing of femurs

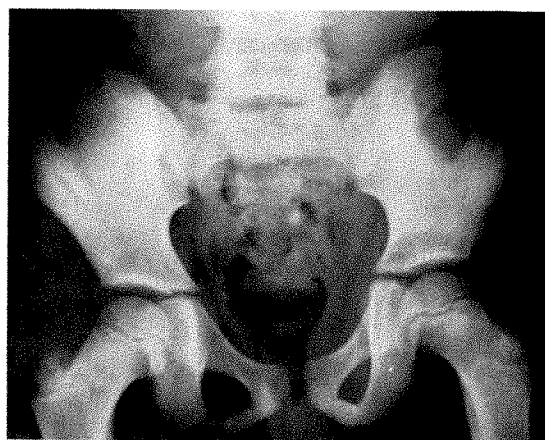


FIG. 13. Case 6, T. B. III. August 28, 1959. Complete healing of right ilium and partial healing of left ilium.

compounds in the investigational category. Their value, in our opinion, has been great in some cases, but poor in others. Further studies in their use are encouraged.

SUMMARY

The clinical features of 62 cases of reticuloendotheliosis in children have been briefly reviewed.

The recognized problems in classification are again emphasized by this survey. The term reticuloendotheliosis, however, is broad enough to include all clinical manifestations of these pathologic entities irrespective of the site or sites involved, the acuteness or chronicity of the process or the final result. The descriptive subclassifications "solitary," "disseminated," and "malignant" might be less confusing to the clinician than the terms "eosinophilic granuloma," "Hand-Schüller-Christian disease" and "Letterer-Siwe disease."

The younger age groups were principally affected. Only 12 children were over 5 years of age and more than half of the remaining 50 were under 2 years. The male to female ratio was 3:2.

The diagnosis was made very promptly in many instances. In others, delays of months occurred.

The clinical course of these patients varied from acute to prolonged chronicity. In the age group under 2 years, the granulomas were usually more disseminated and the children more seriously ill. The persistence of osseous lesions, or the development of new defects while old lesions were resolving, was not incompatible with recovery in some cases.

The suspicion that many of these conditions are due to an infectious agent or its products is supported by the fact that in 2 cases discussed,^{14,19} a bacillus was cultured from the lesions. Furthermore, the satisfactory results from the use of antibacterial drugs in these 2 children and in 4 others in whom no bacteriologic confirmation was obtained lends additive credence to the hypothesis that a microorganism is involved in the pathogenesis. It will be re-

TABLE VII
RETICULOENDOTHELIOSIS THERAPY

Solitary	Disseminated/Malignant/ "Variants"
Biopsy	Biopsy
Curettage	Chemotherapy
Roentgen	1. HN ₂ and/or steroids
Therapy	2. Antimetabolites (6 mo. constant) steroids ±
	3. Antimetabolites (cyclic) steroids ±
Chemotherapy	4. Antimicrobials ±
(6 mo.)	Roentgen therapy—local "hazardous" sites
	Surgery—complications

called that the immunologic status of many young infants is not able to cope with many common infections. Furthermore, it is possible for some usually nonpathogenic organisms to adopt a pathogenic quality if host and environmental conditions permit.

Recommended methods of treatment have been outlined. The prognosis is so variable that irrespective of the histologic findings, the clinical course, observed over a period of several months, will best disclose what the ultimate outcome will probably be.

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THE SUPERIOR MEDIASTINAL SYNDROME IN CHILDREN WITH CANCER *

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COMPRESSION of the structures within the superior mediastinum leads to venous engorgement, cyanosis, edema of the head and neck, stridor, and dyspnea. This combination of signs and symptoms is termed the superior mediastinal syndrome, and is very similar to the superior vena caval syndrome where venous obstruction is the predominant pathology.

The superior mediastinal syndrome is seldom encountered in children with cancer. Only 9 patients, all boys, presented with this picture among the 607 patients under 17 years of age, with malignant disease exclusive of leukemia, who were treated at The Children's Hospital and The Children's Cancer Research Foundation in the 6 years, June 1, 1956 to May 31, 1962 (Table 1). Compression of the superior mediastinal structures may develop insidiously so that the patient may have few relevant complaints; nonetheless, these children are in jeopardy. Complete venous blockade or total obstruction of the airway can develop with dramatic suddenness, as is illustrated by the following case report.

CASE 1. C.C. This 14 year old boy developed a sore throat and cervical lymphadenopathy 3 weeks before admission to the hospital. He was treated with antibiotics, with a diagnosis of tonsillitis. A few days before admission, pink spots were noted on the legs, and frank hematuria became manifest. Cough and wheezing had also developed, but the child did not appear to be in respiratory distress. Hepatosplenomegaly was present. Laboratory studies revealed a white blood cell count of 1,000 cells per cubic millimeter, and a peripheral blood

smear showed a decrease in platelets and 74 per cent blast forms. A roentgenogram of the chest showed a large mediastinal mass compressing the trachea to a narrow ribbon. As the roentgenologic examinations were being performed, he suddenly became deeply cyanotic and stopped breathing. He was revived, received hydrocortisone, but died the next day.

The child with the superior mediastinal syndrome constitutes a medical emergency. Measures necessary for early diagnosis should be undertaken without delay. Although definitive diagnosis may only be established by biopsy of the mediastinal tumors, these patients frequently pose too grave an anesthetic risk to make any but the simplest procedures possible. Physical examination and roentgenograms of the chest, abdomen, and skeleton can lead to tentative diagnoses, while examinations of the peripheral blood, bone marrow, or biopsy of an accessible enlarged lymph node may be diagnostic. None of these studies require general anesthesia. On occasion, however, they are not conclusive. Despite this, it may be necessary, because of the urgency of the problem, to proceed with therapy on the basis of a roentgen and clinical diagnosis alone. Early, vigorous treatment, designed to cause rapid shrinking of the tumor, should not be delayed by an overly-diligent pursuit of the diagnosis.

INITIAL TREATMENT

Simultaneous chemotherapy and radiation therapy are now employed in all cases, to ensure rapid regression of the tumor.

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From The Children's Cancer Research Foundation, the Department of Radiology, The Children's Hospital and Harvard Medical School, and the Department of Medicine, The Children's Hospital, and the Department of Pediatrics, Harvard Medical School.

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CHEMICAL AND HORMONAL THERAPY

1. When lymphosarcoma is proved by biopsy, or strongly suspected, intravenous hydrocortisone, 8 mg./kg. body weight, is given in the first 24 hours. An oral steroid (prednisone, 2 mg./kg./day) is substituted

thereafter, as the clinical condition improves.

2. When it cannot be decided whether the patient suffers from lymphosarcoma or Hodgkin's disease, nitrogen mustard is added at a dose level of 0.2 mg./kg. of body

TABLE I

Case	Name	Sex	Age (yr.)	Initial Diagnosis	Presenting		Initial Treatment	Tumor Response	Survival from Onset*	Remarks
					Symptoms	Signs				
I	CC	M	14	Lymphosarcoma; acute leukemia	Cough and wheeze; sore throat	Cervical lymphadenopathy; petechiae; hematuria	—	—	3 wk.	Expired within 24 hr. of diagnosis
II	PD	M	14	Lymphosarcoma	Cough and dyspnea; tender lumps in scalp	Cyanosis; cervical and inguinal lymphadenopathy; masses in scalp	Simultaneous ACTH and roentgen therapy	Rapid and complete in 4 days	10 mo.	Leukemia terminally
III	TB	M	16	Lymphosarcoma	Cough and dyspnea; dysphagia	Palpable mass in suprasternal notch	Sequential: surgery; nitrogen mustard; ACTH; chlorambucil; roentgen therapy	Slow and complete in 20 days	13 mo.	Leukemia terminally
IV	WM	M	12	Lymphosarcoma	Dyspnea	Lymphadenopathy; hepatosplenomegaly; testicular enlargement	Simultaneous ACTH and roentgen therapy	Prompt and complete in 14 days	10 mo.	Rapid relief of respiratory symptoms; leukemia terminally
V	TB	M	12	Lymphosarcoma; acute leukemia	Dyspnea	Dyspnea; lymphadenopathy; right facial palsy	Simultaneous cortisone and roentgen therapy	Rapid and complete in 4 days	6 mo.	Bone marrow remission in 7 days
VI	JP	M	14	Hodgkin's disease	Cough; anorexia; fatigue and weight loss	Dyspnea; right pleural effusion	Sequential: ACTH; roentgen therapy; chlorambucil	Slow and incomplete	21 mo.	
VII	JS	M	4	Malignant lymphoma	Cough and dyspnea; chest pain and fever	Dyspnea; cyanosis; left pleural effusion; generalized lymphadenopathy	Sequential ACTH and roentgen therapy	Slow and incomplete	9 mo.	Slow but steady relief of respiratory distress
VIII	KB	M	4	Malignant lymphoma	Dyspnea; sore throat; fever	Dyspnea; left pleural effusion; mild proptosis	Sequential cortisone and roentgen therapy	Slow and complete in 7 days	3 mo.	Rapid relief of respiratory symptoms
IX	RC	M	2	Neuroblastoma	Fever and irritability	Tachypnea; cyanosis; proptosis; periorbital ecchymosis	Simultaneous nitrogen mustard and roentgen therapy	Slow and incomplete	21 mo.	Rapid relief of respiratory signs

* All patients dead.

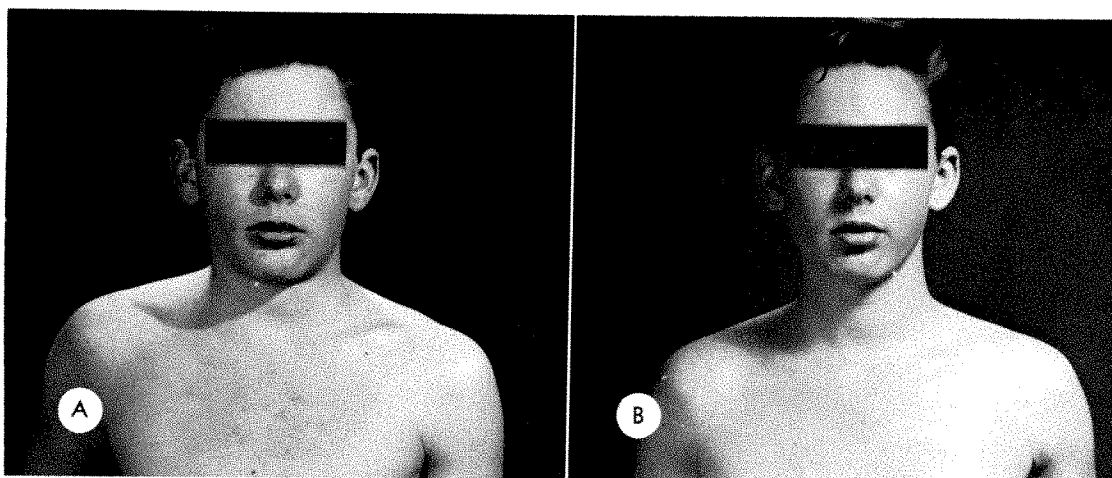


FIG. 1. Case II. (A) Appearance on admission to the hospital. There is edema of the face and neck (with narrowing of the palpebral fissures) and fullness of the neck. The lateral transthoracic diameter is increased and the ribs are prominent, reflecting pronounced emphysema. (B) After treatment. There is striking difference in the facies and habitus, once the superior mediastinal structures have been relieved of compression by the tumor.

weight for 2 consecutive days.

3. When a nonlymphomatous neoplasm is suspected or proven, an appropriate chemotherapeutic agent is chosen. For example, nitrogen mustard is given for neuroblastoma.

RADIATION THERAPY

At this institution, factors yielding a half value layer of 2.7 mm. of copper are employed. The field is designed to encompass all the tumor. The initial mid-plane depth dose ranges from 10 to 50 r, depending on the diagnosis and the degree of tracheal compression demonstrable roentgenographically. If the first dose is tolerated well during the ensuing 6–8 hours, another and similar treatment is given. The tumor dose is doubled thereafter until a single tumor dose of 150 r is being delivered. By the time this dose is attained, most children with lymphosarcoma have improved dramatically.

ANCILLARY MEASURES

Rapid response to therapy may result in hyperuricemia and uric acid nephropathy.⁴ Measures should be taken to prevent this complication. It is essential to ensure ade-

quate hydration, and to alkalinize the urine. Potassium bicarbonate or citrate is given in preference to the sodium salts, when steroids are being administered.

RESULTS

The results obtained in children managed in this fashion are illustrated by the following case report.

CASE II. P.D. This 14 year old boy had been well until he noted some lumps on his scalp. These increased in size and became tender. A biopsy of one of the lesions revealed lymphosarcoma. He then developed a cough, dyspnea, and a bluish discoloration of his face and chest. On admission to The Children's Hospital Medical Center, there were findings consistent with the superior mediastinal syndrome (Fig. 1A). Enlarged lymph nodes were palpable in the neck and right inguinal region. Over the surface of the scalp were several masses, all of them freely movable and not attached to the skull. They averaged 1.5 cm. in diameter and were firm to palpation. Chest roentgenograms showed a huge mass compressing the mediastinal structures (Fig. 2, A and B). Examination of the bone marrow revealed normal findings. Treatment was initiated on admission to the hospital. He received simultaneous ACTH intravenously (20 units daily) and radiation

therapy. The mediastinum was given 10 r tumor dose in the morning. This was tolerated well and a similar treatment was given in the afternoon. The dose was increased gradually so that by the third treatment day, a total (mid-plane) dose of 213 r had been accumulated. By this time the scalp and inguinal masses had disappeared and a chest roentgenogram showed complete clearing of the mediastinal tumor (Fig. 2, *C* and *D*). A striking difference was also noted in the facies and habitus (Fig. 1*B*).

All patients with lymphosarcoma, treated

with combined hormone and radiation therapy, responded rapidly, clinically and radiologically. When combined treatment was not employed, the tumor regressed more slowly, as shown in Case III.

CASE III. T.B. This 16 year old boy was well until he began to complain of a mild cough. His symptoms increased in severity and dyspnea and dysphagia became marked. Two weeks after the onset of symptoms, he was admitted to another hospital, in severe respiratory distress. A mass was palpable in the supra-

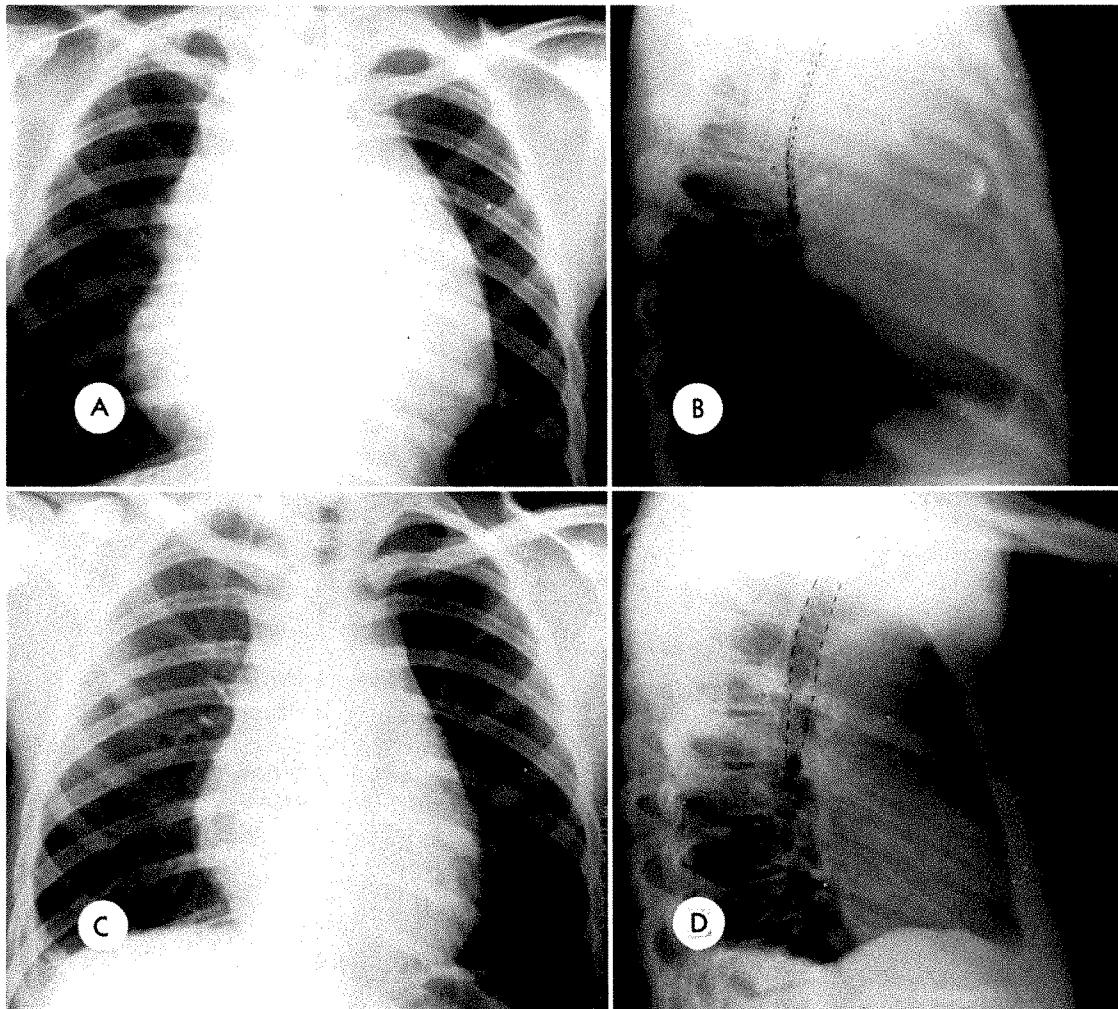


FIG. 2. Case II. (*A* and *B*) December 31, 1958: There is a huge mass filling the anterior and superior mediastinum. The trachea is markedly compressed from the anterior aspect, and is displaced posteriorly. The lungs are emphysematous. (*C* and *D*) January 2, 1959: Two days later there is almost total disappearance of the tumor, with return of the trachea to normal caliber. The lungs are no longer emphysematous, but fluid is present in the right pleural cavity.

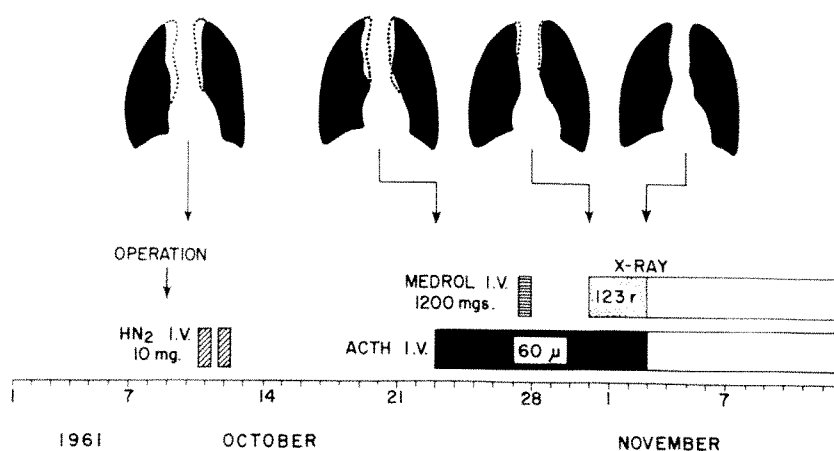


FIG. 3. Case III. Sequential therapy of mediastinal lymphosarcoma. Schematic representation of roentgenographic changes in relation to the timing of administered treatment.

sternal notch. A chest roentgenogram showed a soft tissue mass in the superior mediastinum surrounding the trachea. An operation was performed on the second hospital day. The mediastinum was entered through a sternum-splitting incision, a small amount of the underlying tumor was removed, and a tracheotomy tube was inserted. A diagnosis of lymphosarcoma was made by microscopic examination of the specimen. On both the 2nd and 5th postoperative days, he received 10 mg. (0.2 mg./kg. body weight) of nitrogen mustard. His respiratory symptoms improved, although a roentgenogram 3 days later showed only partial shrinking of the mediastinal mass. He was transferred to The Children's Hospital Medical Center on the 14th postoperative day.

Roentgen examination of the chest showed persistence of the mediastinal mass. Therapy with ACTH (60 units parenterally) was initiated and continued during the next 14 days. A single large dose of "medrol" (1,200 mg.), intravenously, was added. On the 8th day in the hospital, a long course of radiation therapy to the mediastinum was started. Gradual improvement followed (Fig. 3).

This boy required 20 days of treatment before the chest roentgenograms became normal, unlike Case II, in which the same result was achieved after 4 days of combined therapy.

DISCUSSION

Mediastinal masses are not uncommon in children with malignant diseases, but few develop the superior mediastinal syndrome.

The 9 boys reported here are examples of a rare complication of childhood cancer. Eight had lymphoma, which comprises about 6.5 per cent of the 124 patients with lymphoma seen in this institution in the period under study. This frequency is similar to that reported by Rosenberg *et al.*,⁹ but less than that recorded by others.^{1,10} Six of the 8 patients with lymphoma and the superior mediastinal syndrome were over 11 years of age (Table 1). Many younger children have intrathoracic masses which displace the mediastinal structures, but apparently they seldom develop the signs and symptoms of superior mediastinal syndrome.^{6,7} Lymphosarcoma is much more common in boys than girls, and it is perhaps not surprising that all the cases presented here were males.⁹

Malignant neoplasms other than lymphoma can also lead to constriction of the superior mediastinal structures.⁷ Alternate diagnostic possibilities should be kept in mind so that treatment can be made as specific as possible. Case IX (R.C.) illustrates this point. He had periorbital ecchymoses when first examined. This sign, in a child of 2 years, together with the roentgenographic findings, virtually established the diagnosis of disseminated neuroblastoma and treatment was started without further delay (Fig. 4, A and B). Bone

marrow aspiration subsequently confirmed the diagnosis.

Mediastinal masses in association with the superior mediastinal syndrome threaten life and can precipitate a serious medical emergency with little if any other warning. Case I was an example of the rapidity with which respiratory obstruction can develop. Establishing a working diagnosis at the earliest moment is highly desirable so that vigorous treatment, designed to secure the rapid dissolution of the constricting masses,² can be started. In our opinion, this can best be accomplished by combining irradiation with simultaneous hormonal and chemotherapy. When the two modalities are employed in sequence, the tumors seem to respond less promptly (Case III). The simultaneous use of corticosteroids has an additional advantage because of their "anti-inflammatory" effects which would tend to reduce the advent of postradiation edema.

Superior vena caval obstruction and its management in adults was the subject of a recent symposium.¹¹ Lung cancer was the

most common underlying lesion. It is not easy to relate the experience described regarding radiotherapeutic dosage regimens and the role of hormones and chemotherapeutic agents to children in whom the lymphoma group is most frequently represented, and in whom tracheal rather than vascular compression represents the major hazard.

Green, Rubin and Holzwasser⁵ produced superior vena caval obstruction by growing a transplantable tumor in the mediastinum of rats. A well-planned series of experiments was then conducted to evaluate the effects of radiation, given according to a variety of dose schedules. (The survival of animals treated with nitrogen mustard and corticosteroids alone and in combination with roentgen therapy was also studied.) These investigators conclude, on the basis of these experiments, that: (1) postradiation edema within tumors is not a cause for concern since any that may occur is offset by concomitant tumor shrinkage; (2) prolonged low dose therapy, to avoid this complication, therefore, is not necessary;

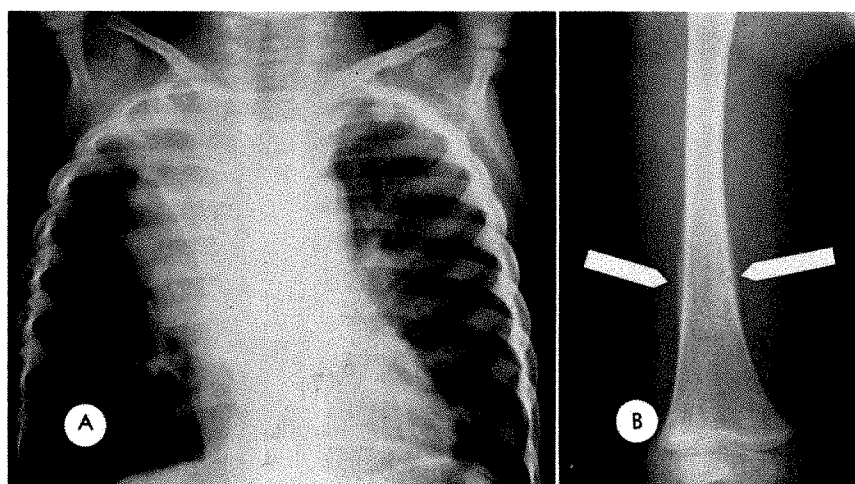


FIG. 4. Case IX. (A) Frontal roentgenogram of the chest. There are irregular masses visible to either side of the midline structures. The second right rib is thinned and notched in its posterior aspect, and the second interspace is widened. The trabecular pattern of the ribs is abnormal, as seen in their axillary portions on the right. (B) Frontal roentgenogram of the right femur. There is subperiosteal new bone formation along the femoral shaft (arrows) in association with mottled rarefaction, centrally. The presence in a child of an intrathoracic paravertebral mass, not of recent origin, with metastases to the skeletal system and mediastinal lymph nodes is strongly suggestive of neuroblastoma. When coupled with the clinical picture in this case, the diagnosis became almost certain.

(3) protracted low dose regimens do not give as good control as rapid high dosage techniques; and (4) rapid, high dose therapy is safe and more likely to secure a good clinical result.

We agree that prolonged low dose radiation therapy is unnecessary and potentially self-defeating because a radio-insensitive tumor might well progress during the course of overly cautious treatment regimens. On the other hand, although originally skeptical, we now have little doubt that irradiation of various tissues can lead to local edema. It has long been stated that children receiving roentgen therapy of the nasopharynx because of regional lymphoid hyperplasia occasionally develop bilateral swollen parotid glands.⁸ Our experience has been similar, the change taking place within hours following the delivery of 200 r or less. Return to normal occurs within a similarly short time. We can find no explanation for this phenomenon other than postradiation swelling of the parotid gland. We also have seen pronounced enlargement of cutaneous hemangiomas after doses of about 200 r. Two infants with glottic hemangiomas and narrowed airways developed respiratory distress after radiation treatment. Both became severely dyspneic 6-8 hours after delivery of about 150 r (tumor dose) to the larynx. Tracheal occlusion occurs with this lesion spontaneously, so it cannot be stated with assurance that radiation therapy precipitated the complication. We have not, however, seen this again since we instituted a therapeutic regimen similar to that outlined above.

In summary, we believe that the radiation therapy technique here advocated minimizes any potential risk without undue compromise in speed. The hours of treatment are selected so as to ensure that any respiratory distress associated with therapy will not occur during the early morning hours. It is then that acute respiratory embarrassment more readily escapes notice. The critical time interval seems to occur 6 to 8 hours after treatment, as judged from

our experience with the 2 children with laryngeal hemangiomas, described above. It is also our practice to alert our colleagues on the surgical staff so that they will be thoroughly conversant with the problem, and can make appropriate preparations.

Hydrocortisone and ACTH have both been employed in the management of patients with lymphosarcoma. Equally good results have been obtained with either agent. Since it is the adrenocortical preparation which leads to lympholysis,³ we have more recently used intravenous hydrocortisone, by preference.

The combined treatment outlined above is tolerated well by the children, and is designed to procure rapid regression of the constricting tumor masses. Although the prognosis is grave in all these patients (Table 1), the initial results of treatment are very gratifying and severe respiratory distress often can be relieved within hours.

SUMMARY

Nine children with the superior mediastinal syndrome secondary to a malignant disease are reported. This rare complication, most often seen in patients with lymphoma, constitutes a medical emergency. It often responds promptly to treatment with simultaneous chemotherapy and radiation therapy.

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UNUSUAL BENIGN AND MALIGNANT SEQUELAE TO CHILDHOOD RADIATION THERAPY*

INCLUDING "UNILATERAL HYPERLUCENT LUNG"

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THE report by Arkin *et al.*¹ in 1950 of an unusual case of scoliosis and lumbar vertebral deformity in a 13 year old girl, who had received postoperative radiation therapy for a Wilms' tumor at the age of 19 months was the first of a number of reports concerning postradiation bone changes in survivors of childhood tumors.^{17,24,27,28}

Growth disturbance not only in regions but also in individual bones, exostosis formation^{6,8,16,17} and muscle hypoplasia have been noted in longitudinal bone studies of children treated with radiation early in life for malignant as well as benign disease.

These clinical observations have been matched by experimental production of similar dysplastic changes by radioactive isotope administration, both systemically²⁵ and locally adjacent to growth centers,² and by external radiation to a growth center.²³

A review of our own experience with long term survivors following childhood radiation therapy, plus a review of published cases, suggests some of the following generalizations:

1. The more growth potential a bone has, the more it is apt to show the effect of the radiation on orderly bone formation and growth; *i.e.*, an iliac bone will show more change than a rib, a femur more than a fibula.

2. Time is required in order to develop these changes. Short term survivors will obviously not grow enough to manifest them.

3. Dosage levels roughly parallel the radiation effect. Because the higher doses, usually over 2,000 r tumor dose, were given

for malignant disease, the survivors in this group showed the most severe changes.

4. Where the primary disease involved bone, radiation effects were more pronounced.

5. The spine grows, as do long bones, by enchondral bone formation.⁴ Both sites showed growth retardation and distortion; the long bones also showed neoplasia with osteochondroma formation. No known malignant transformation has been observed in such postradiation exostoses to date.

6. Radiation induced malignancy in children was seen, osteogenic sarcoma developing in a survivor of retinoblastoma. Such sarcomas have been associated, in general, with high dosage, exceeding 4,000 r tumor dose. This amount has been employed in children most commonly when small portals were irradiated, *i.e.*, orbital lesions.

Examples illustrating these changes, plus an unusual case of "unilateral hyperlucent (transradiant) lung," which developed in a survivor of metastatic Wilms' tumor are presented. All patients, unless otherwise noted, were treated with orthovoltage roentgen therapy: 200–220 kv., half value layer 0.9–1.0 mm. copper.

WILMS' TUMOR

A review of 42 patients with Wilms' tumor seen at Babies Hospital between 1934 and 1956,¹² treated with surgery and postoperative irradiation, showed that the prognosis improved when the diagnosis was made at an early age; children treated before the age of 2 years had a significantly

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better survival rate than older patients. Also, radiation changes appear to occur more often in the younger patients, primarily because the older children did not survive long enough to exhibit the radiation dysplasias.

Wilms' tumor patients (Fig. 1, *A*, *B* and *C*) were treated at Babies Hospital through large anterior and posterior portals that crossed the midline and included the ipsilateral iliac crest with its apophysis. In 10 of the 42 patients, serial abdominal roentgenograms showed progressive iliac and vertebral growth changes. The true incidence of these changes in survivors is not known since in some cases only chest roentgenograms were made on follow-up, while others were lost to follow-up.

As well described by Neuhauser and his colleagues¹⁷ in 1952 and in several recent reports,^{24,27} the radiation effects present on serial roentgenograms show a retarded and distorted growth pattern. Subcortical lucent zones progress over a period of months to subcortical growth arrest lines, showing a "bone within a bone" pattern. The "bone within a bone" is approximately the vertebral size at the time of therapy. The bodies

are bulbous. As growth continues, the bodies become diminished in height and irregular in shape, with anterior-inferior and superior defects at the site of the rim of the apophysis. In a manner, these findings are virtually identical to those of spondylo-epiphyseal dysplasia (Morquio-Brailsford) and cretinism. Even though the portals cross the midline, the half of the body on the side of the tumor shows maximum effects, due probably to a combination of distorted muscular stress and some fall-off in dosage.

A previously unrecognized radiation effect in children appeared in one of the patients in the form of a "hyperlucent lung."

ILLUSTRATIVE CASE

CASE I. An 8 week old female was treated in 1952 for a rightsided Wilms' tumor by nephrectomy, followed by a 3,300 r tumor dose to the right abdomen. Ten years later vertebral and iliac hypoplastic and dysplastic changes were noted (Fig. 2, *A* and *B*) with the final appearance of a moderate scoliosis, a small right ilium, and hypoplastic right paraspinal musculature.

Ten months following nephrectomy, a large right middle lobe mass extending to the pleural

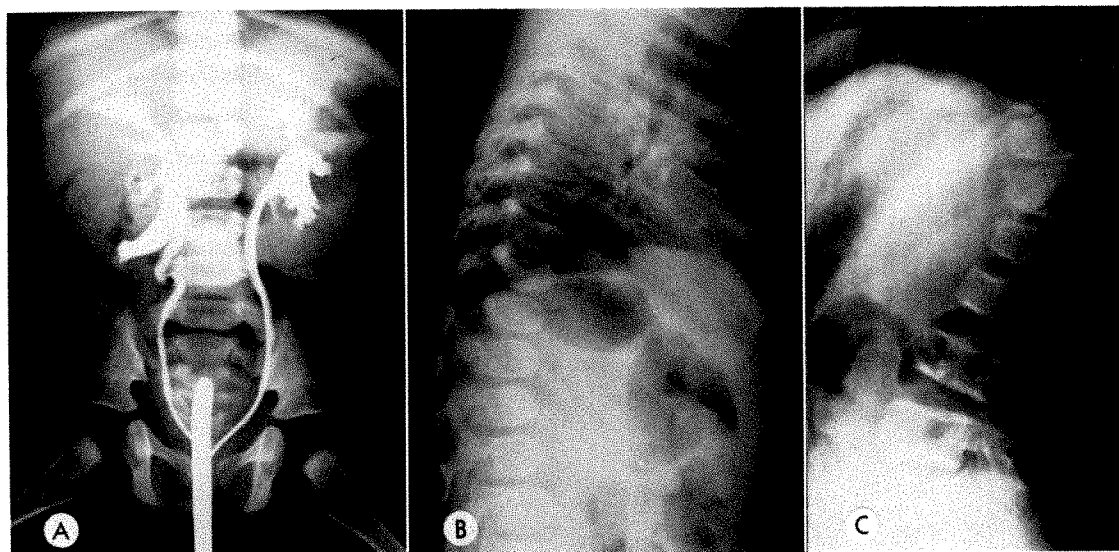


FIG. 1. Rightsided Wilms' tumor in an 8 month old girl.

(*A*) Normal lumbar spine and pelvis before 3,000 r postresection radiation therapy was given. (*B*) Ten months later, follow-up roentgenogram shows bulbous lumbar centra. (*C*) Ten years later, flattened, irregular and hypoplastic lumbar centra have developed with mild kyphoscoliosis.

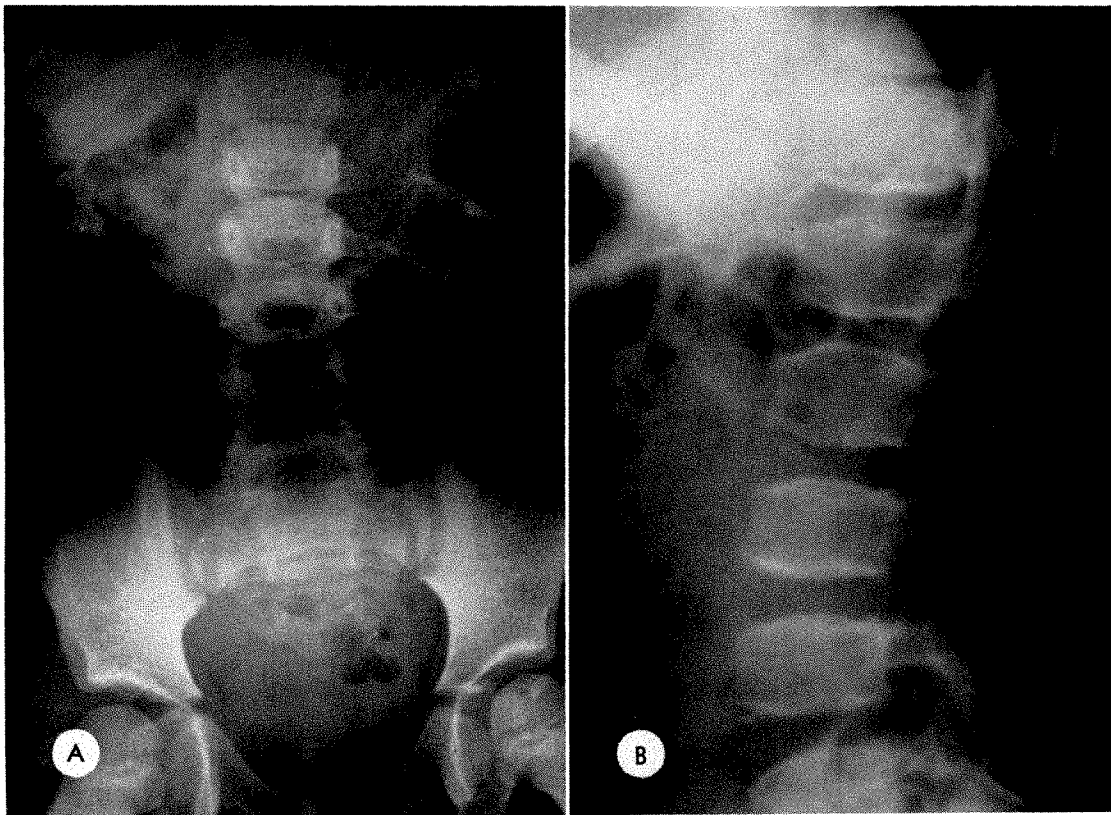


FIG. 2. Case 1. Rightsided Wilms' tumor in an 8 week old girl. A dose of 3,300 r was given after resection. (A) Ten years later, the lumbar spine and pelvis show both distorted contour and hypoplasia. (B) Lateral roentgenogram of the lumbar spine shows irregularity and flattening of the centra.

surface was detected. Lateral roentgenogram of the spine at this time revealed postradiation bulbous centra and a "bone within a bone" appearance (Fig. 2C). A tumor dose of 1,500 r was delivered to the entire right lung with the scapula and mediastinum within the therapy portal. Within 3 years (Fig. 2D) and progressively since then, the right lung has become hyperlucent with diminished vasculature. The right hemithorax is smaller than the left, with a mediastinal shift to the right. A right osteochondroma of the scapula tip is now present. The decreased vasculature was confirmed by venous angiocardigraphy (Fig. 2E).

Following angiocardigraphy, symptoms suggesting intra-abdominal inflammatory disease led to a gallbladder and a small bowel contrast study (Fig. 2F). Findings resembling a diffuse ileitis were seen in the right side of the abdomen within the portal of irradiation. The patient's symptoms disappeared on antispasmodic therapy.

Comment. Lumbar hypoplasia with iliac distortion is not unexpected following a dose of 3,300 r in infancy. All radiation effects in this patient were within the treated areas. During 10 years of follow-up, the growth of the patient magnified this radiation effect. The gradual appearance of a transradiant or hyperlucent lung as a complication of irradiation has not previously been reported. Prior reports of this unexplained entity^{7,11,15,18,20,21} have stressed recurrent childhood respiratory infections; our patient had one episode of right middle lobe pneumonia in 1957.

Some patients with hyperlucent lung have demonstrated on pulmonary function studies^{7,21} increased residual lung volume and elevated pulmonary wedge arterial oxygen levels. Several have been operated upon because of hemoptysis.¹⁸ Although

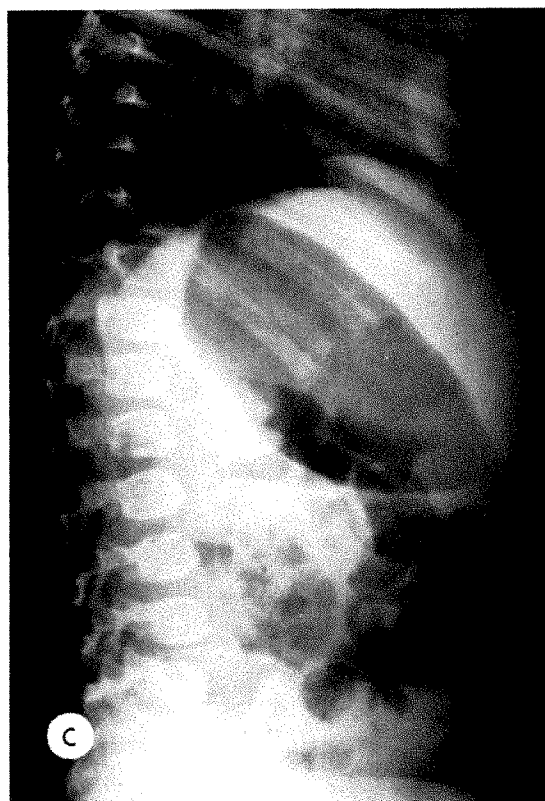


FIG. 2. Case 1. Ten months after resection and radiation therapy, a right middle lobe metastasis developed.

(C) Lateral roentgenogram of the spine at this time revealed postradiation bulbous centra and a "bone within a bone" appearance.

angiocardiograms revealed sparse filling and even nonfilling of the pulmonary arteries, patent pulmonary vessels with enlarged bronchial arteries have been found at surgery. It has been suggested that bronchial artery-pulmonary artery shunts account for the high oxygen levels and for failure of the pulmonary vessels to opacify on right sided angiocardiography.²¹

Our patient had not only radiation damage and pneumonia, but also a metastatic lesion. Liebow *et al.*,¹⁴ in addition to studies on bronchial artery shunts in bronchiectasis, demonstrated a bronchial supply to primary and metastatic malignancy.¹³ We feel that the increase of a bronchial artery supply from the neoplasm could be added to the radiation inflammatory change in a patient with at least one known episode of

pneumonia. This could also account for vascularization during healing. Such processes are capable, in view of Liebow and his co-workers' work,¹⁴ of opening up bronchopulmonary shunts. The high bronchial artery pressure may produce a "counter-flow" effect between the pulmonary and bronchial circulation which can be detected by angiocardiography and by the pressure changes in the pulmonary artery of such patients. Catheterization data supporting such a relationship have been reported.²¹

NEUROBLASTOMA

Since 1932, 84 children with neuroblastoma have been seen at Babies Hospital. Prognosis has again been better in patients

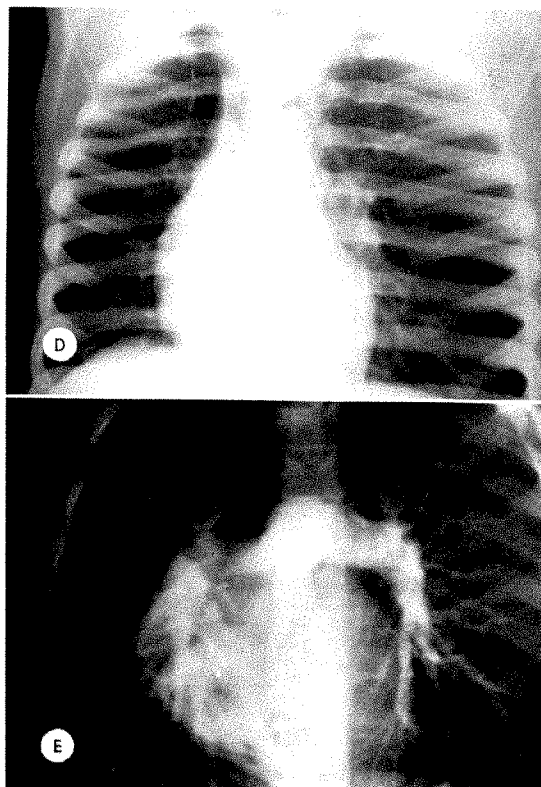


FIG. 2. Case 1.

(D) Three years after chest radiation therapy (1,500 r) for the metastasis, a right scapular exostosis is present and the right lung shows hypovascularity and hyperlucency with mild mediastinal shift. These findings have become even more pronounced later. (E) Left antecubital venous angiogram confirms the right lung hypovascularity. Major vessel obstruction is absent.

who were diagnosed at less than 1 year of age.¹⁰ Four patients with disseminated disease (*i.e.*, skin, bone marrow, liver and abdominal masses) who were less than 6 months of age at the time of diagnosis are alive and well, 3 to 5 years later.

In contrast to Wilms' tumor, neuroblastoma often invaded and destroyed adjacent bone and cartilaginous structures. We have found, as did Rubin *et al.*²⁴ and Neuhauser *et al.*,¹⁷ that such prior bone damage, when combined with radiation effect, results in the most severe dysplasias, as opposed to the normal bone included within radiation portals in cases of Wilms' tumor.

Figures 3 through 5, inclusive, show typical adrenal and mediastinal tumors. A

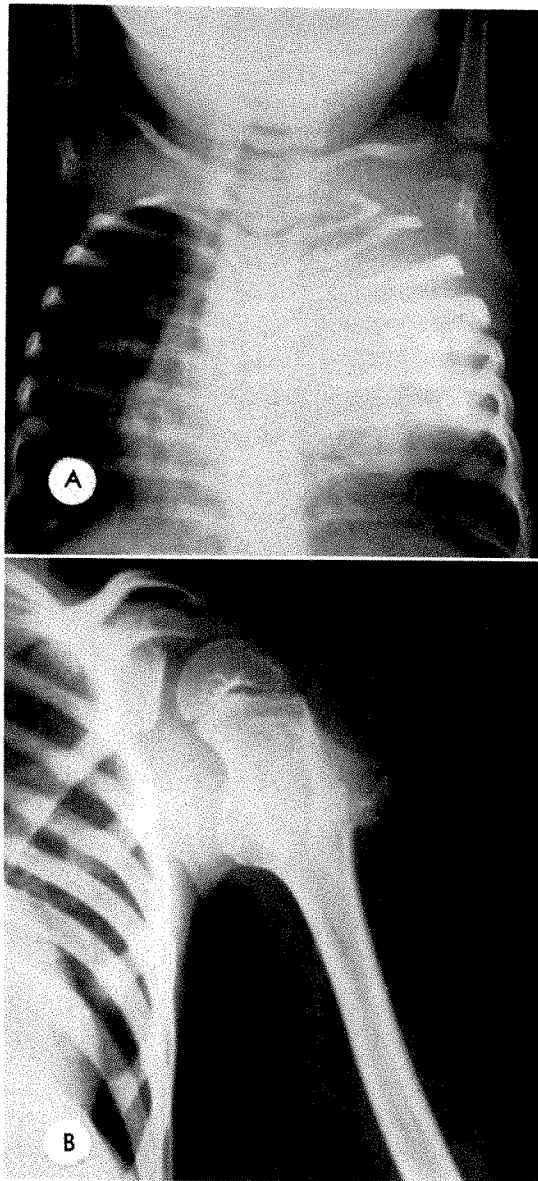


FIG. 3. Neuroblastoma.

(A) A 10 month old boy had had a left posterior mediastinal neuroblastoma which was biopsied, partly excised and treated with 2,500 r tumor dose. (B) Eight years later, a left humeral osteochondroma, which had its inception 2½ years after A, is demonstrated. Although still benign in appearance, it continues to grow and excision is planned.

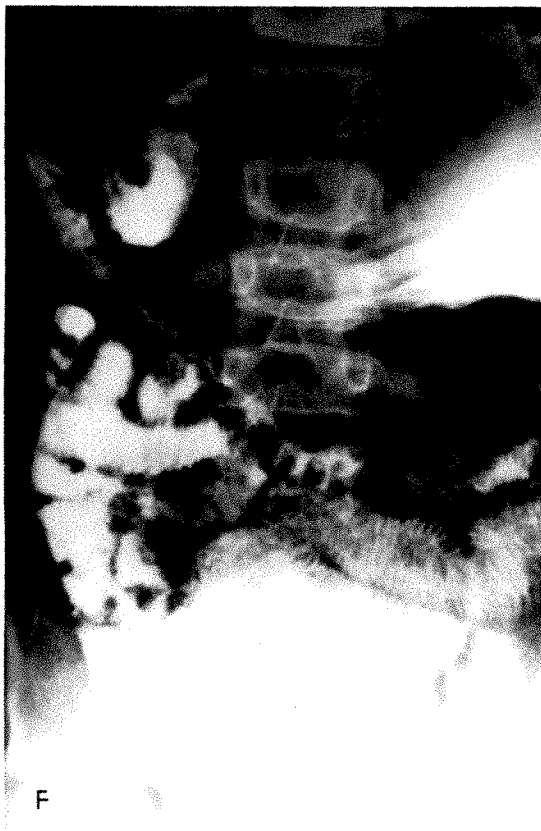


FIG. 2. Case 1.

(F) Small bowel study done several days after E shows ileal loops with spasm, irregular and distorted valvulae, and mild separation of loops, mimicking inflammatory disease and confined to the portal of irradiation.

celiac syndrome complex in 1 of our patients with an adrenal neuroblastoma disappeared following surgery and radiation therapy. The association of such diarrhea with benign as well as malignant neural

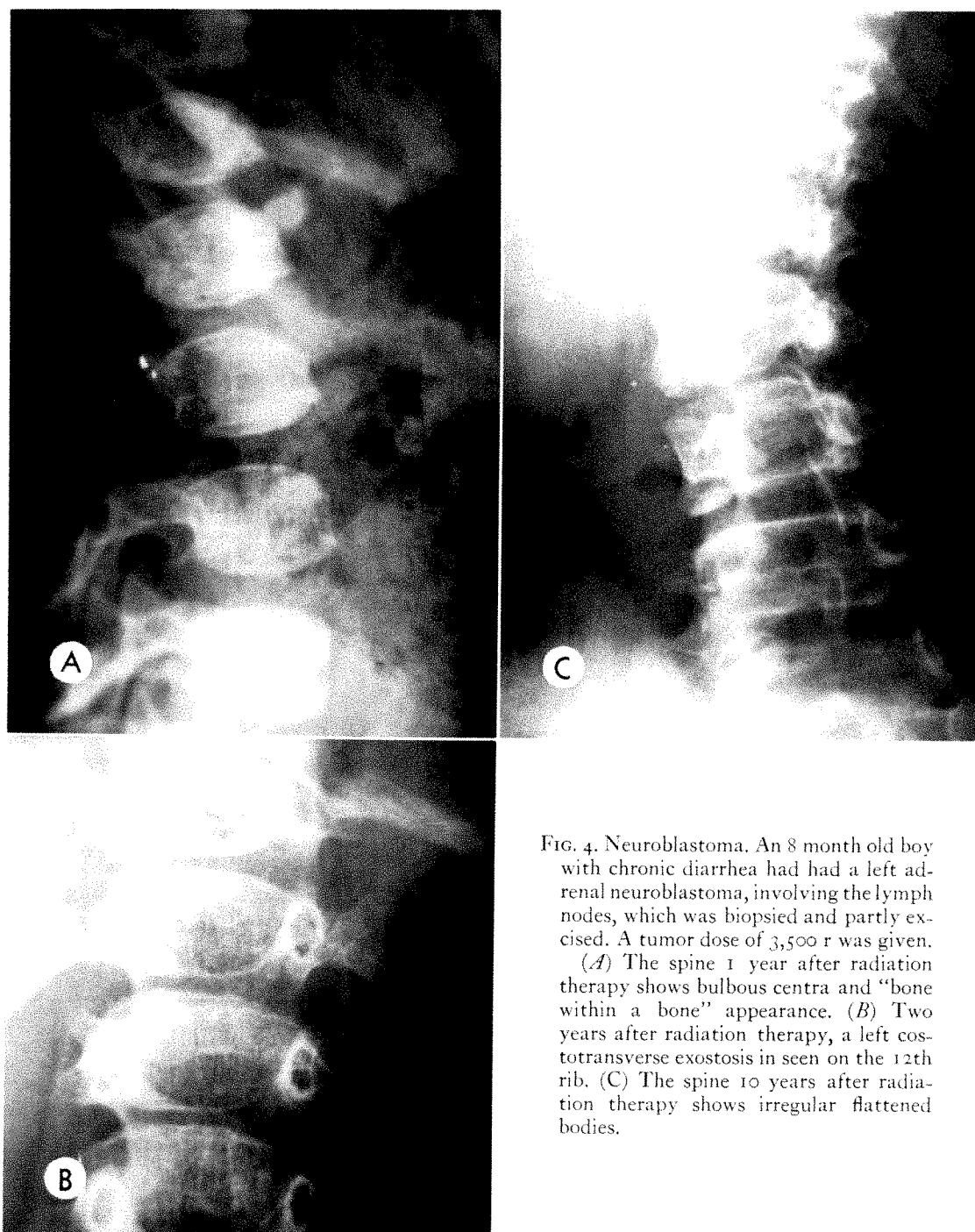


FIG. 4. Neuroblastoma. An 8 month old boy with chronic diarrhea had had a left adrenal neuroblastoma, involving the lymph nodes, which was biopsied and partly excised. A tumor dose of 3,500 r was given.

(A) The spine 1 year after radiation therapy shows bulbous centra and "bone within a bone" appearance. (B) Two years after radiation therapy, a left costotransverse exostosis is seen on the 12th rib. (C) The spine 10 years after radiation therapy shows irregular flattened bodies.

tumors has been discussed recently.²² The exact cause and effect relationship between the increased amounts of catecholamines from the tumor and the diarrhea is not known.

Not only growth disturbances but neoplasia in the form of exostoses was noted (Fig. 3B and 5C). If the bone was originally involved (5B), the scoliosis was severe. It is important to note that the scoliosis in a

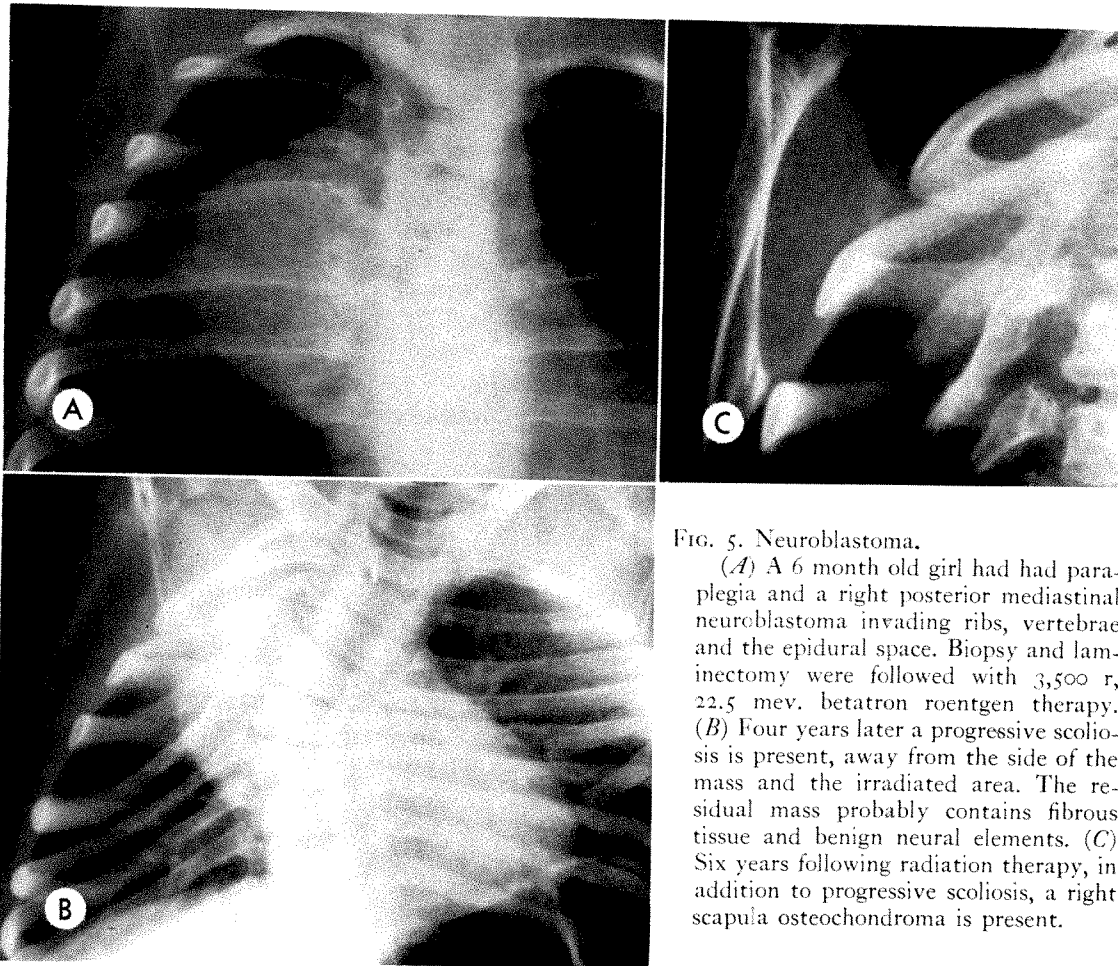


FIG. 5. Neuroblastoma.

(A) A 6 month old girl had had paraplegia and a right posterior mediastinal neuroblastoma invading ribs, vertebrae and the epidural space. Biopsy and laminectomy were followed with 3,500 r, 22.5 mev. betatron roentgen therapy. (B) Four years later a progressive scoliosis is present, away from the side of the mass and the irradiated area. The residual mass probably contains fibrous tissue and benign neural elements. (C) Six years following radiation therapy, in addition to progressive scoliosis, a right scapula osteochondroma is present.

case of a mediastinal neuroblastoma invading the right-sided ribs and vertebral appendages was toward the normal side with spreading of ribs and centra; this is the opposite of the usual radiation effect.²⁴ In addition, radiation changes were present in the centra. Even though the patient was treated with supervoltage 22.5 mev. roentgen rays, bone changes were severe, including a small scapula exostosis (Fig. 5C). The "bone-sparing" properties of supervoltage therapy are real within the small spaces in bone; however, epiphyseal plate cartilage is not "spared." Retarded, distorted and abnormal bone growth resulted regardless of whether ortho- or supervoltage therapy was used. Long term comparisons of results with ortho- and super-

voltage therapy in children are not available.

RETINOBLASTOMA

At Babies Hospital, retinoblastoma involving a single eye is treated by enucleation. When the remaining eye is involved, radiation therapy and, recently, chemotherapy are utilized in an attempt to save the sight. Currently, 22.5 mev. roentgen rays to an average tumor dose of 2,500–3,000 r plus chemotherapy, usually TEM, are employed.⁹ In the late 1940's and early 1950's, however, orthovoltage roentgen therapy was used in very high doses, usually 8,000 r air dose to a lateral temporal and 6,800 r air dose to an opposite nasal oblique field. Forrest⁹ and Reese *et al.*¹⁹ reported post-

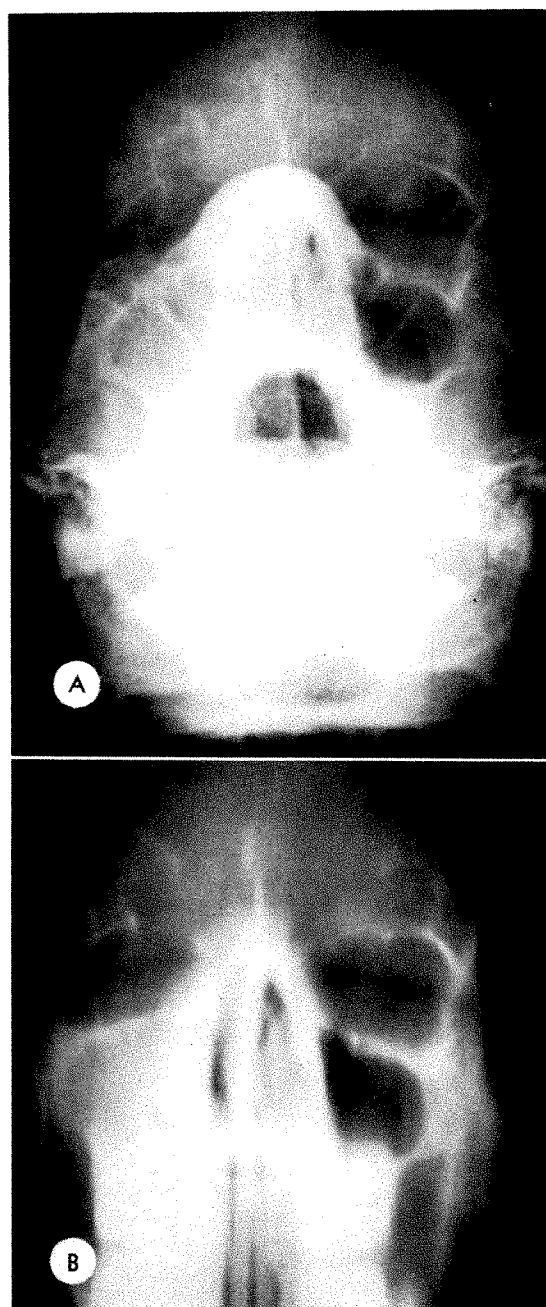


FIG. 6. Case II. Retinoblastoma. A 12 year old boy with bilateral eye enucleation for retinoblastoma. The left eye was enucleated first at the age of 6 months. Four months later radiation therapy was given to the right eye (8,000 r in air to the lateral temporal and 6,800 r in air to the opposite oblique nasal port). Because of suspected recurrence, 3 months later this eye was also enucleated.

(A) A large mass fills the right nasal cavity and the right maxillary sinus is opacified. The orbits

radiation malignancy, usually osteogenic sarcoma or fibrosarcoma, in survivors of such therapy. Malignant transformation was found in 5.3 per cent of the cases. Latent periods as long as 26 years were observed; the average latent period was $6\frac{1}{2}$ years. The dosage in most cases exceeded 5,000 r. No patient survived such a sarcomatous change. An example of a case is presented.

ILLUSTRATIVE CASE

CASE II. The left eye of a 6 month old boy was enucleated in 1950 because of a retinoblastoma. The right eye, normal at that time, was involved with tumor 4 months later. He was treated with 8,000 r in air to the lateral temporal and 6,800 r in air to the opposite oblique nasal port. Three months later, because of a suspected recurrence, the right eye was also enucleated. No tumor was present in the specimen.

The patient was seen infrequently between 1952 and 1962 when he was re-admitted with a large friable bleeding right nasal mass. Several biopsies in the summer of 1962 revealed only necrotic tissue. Eventually, an osteogenic sarcoma was found on curettage (Fig. 6B). Roentgenograms confirmed the right nasal mass by showing opacification of the right antrum and changes secondary to enucleation and radiation (Fig. 6A). No bone destruction or tumor calcification could be seen. The family refused the suggested exenteration and combined radiation therapy with chemotherapy. The child died 4 months later.

At postmortem examination, no residual tumor could be found. A large subfrontal abscess communicating with both the right ethmoid sinuses and the right frontal lobe was present, complicated by streptococcal meningitis.

Comment. The criteria formulated by Cahan *et al.*⁵ for radiation induced malignancy was met in this patient. A suffi-

are small though the right side shows greater hypoplasia and irregularity. (B) Curettage revealed osteogenic sarcoma. Postoperative laminagram confirms the orbital growth changes and shows intact bone walls.

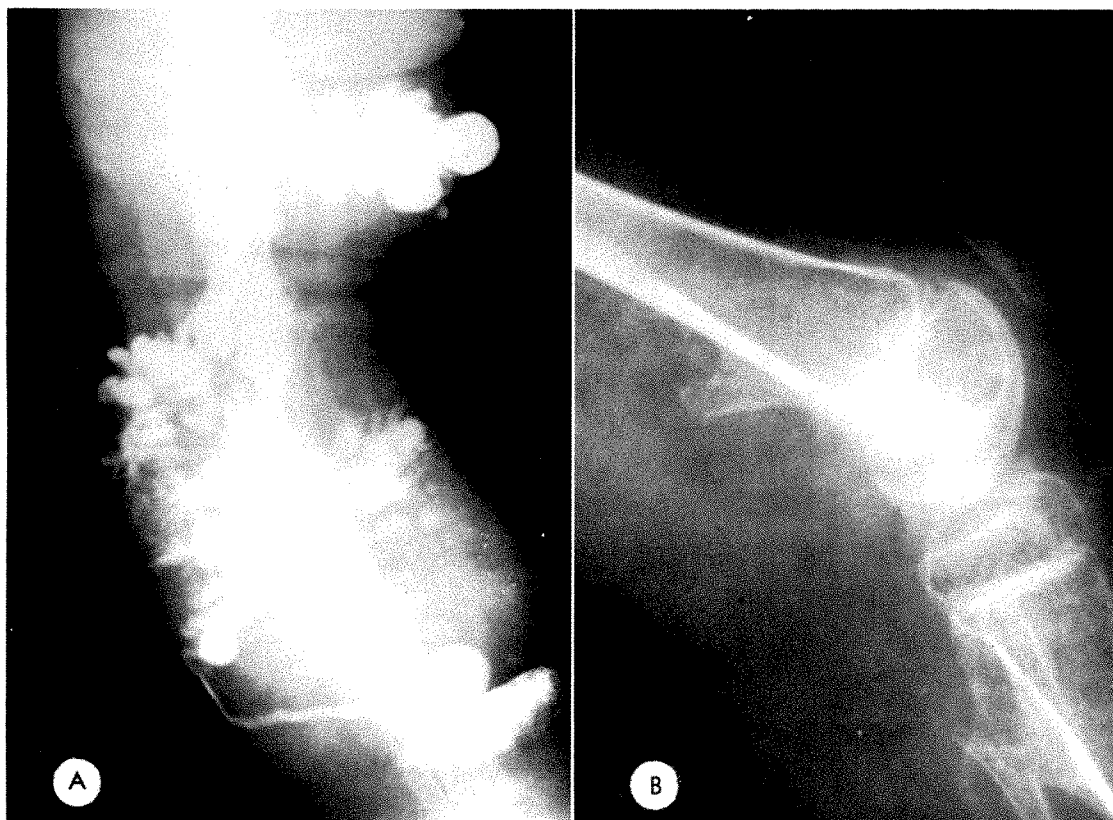


FIG. 7. Cavernous lymphangiohemangioma in an 8 month old girl.

(A) Contrast injection study shows huge tortuous interconnected channels and sinuses. A dose of 1,500 r to the upper leg and 1,200 r to the lower thigh with overlap at the knee had been given. (B) Ten years later, multiple exostoses are present in the femur and tibia (confirmed at excision).

ciently long latent period (10 years) was present. Histologically, the tumor differed from the primary neoplasm (osteogenic sarcoma versus retinoblastoma). The tumor developed within the portal of irradiation; pre-existent benign bone disease capable of giving rise to osteogenic sarcoma spontaneously (*i.e.*, giant cell tumor, Paget's disease) was absent.

Forrest⁹ and Reese *et al.*¹⁹ found 16 cases of sarcomas occurring after radiation treatment of retinoblastoma—an approximate incidence of 6 per cent of those treated and surviving their original disease. This relatively high complication rate may have reflected both the high dosage used previously and the relatively greater bone absorption of orthovoltage energies. Today 22.5 mev. betatron roentgen rays are used

with added chemotherapy; however, it is too soon to state whether this will eliminate such sarcomas in this group of patients. An unusual aspect of Case II is that no residual tumor was found at necropsy examination. Only curettage had been done. There are no reported cases of such radiation induced sarcomas in retinoblastoma survivors having been cured.

HEMANGIOMAS

Hemangiomas, the most common tumor of children, are treated with irradiation today only when severe impairment of function is present (*i.e.*, orbit, palate, nasopharynx), or when platelet trapping is found in association with giant cavernous hemangioma.^{3,26} In the latter group, irradiation has been found to be the best method

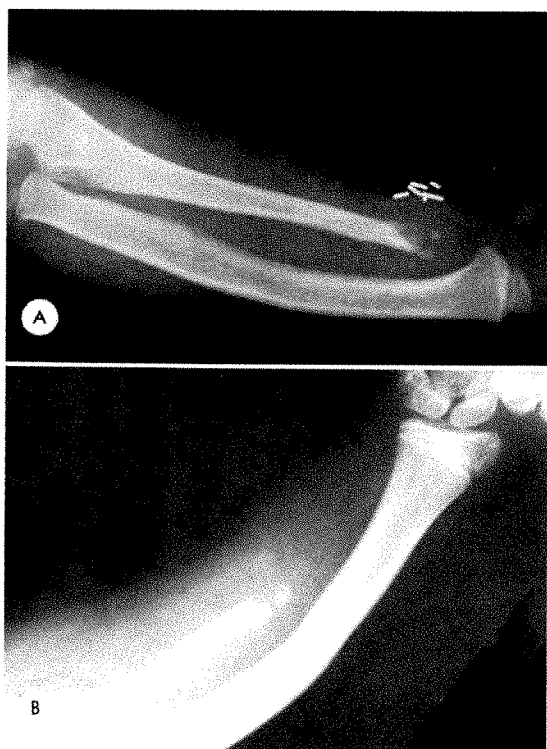


FIG. 8. Large cavernous hemangioma of the left wrist in a girl treated elsewhere at the age of 6 months with 6 radon seeds.

(A) At the age of 4 years, the radius shows early bowing and the end of the ulna is destroyed. (B) At the age of 12 years, there is progressive radial bowing with a pseudo-Madelung deformity. The seeds were removed during a tendon transplant procedure.

of treatment with resulting disappearance of the life-endangering thrombocytopenia and hypofibrinogenemia.

In previous years, many patients received radiation therapy for hemangiomas. Doses were high enough to affect normal osteocartilaginous growth sequence. Growth disturbance and neoplasia (in the form of osteochondromas) resulted. Fanconi and Illig,⁸ Murphy and Blount,¹⁰ and Cole and Dart⁶ reported such exostosis formation following radiation treatment in infancy for cavernous hemangiomas. One of our patients (Fig. 7, A and B) had a cavernous lymphangiohemangioma involving the leg which had been surgically treated without success. Multiple exostoses developed at

sites of epiphyseal bone growth following radiation therapy. One was resected and found to be a benign osteocartilaginous exostosis.

Spiess²⁵ in 1957 reported 3 cases of exostosis formation in children given thorium-X for bone tuberculosis in the late 1940's. The children were 4 to 6 years old at the time of treatment. In serial studies, epiphyseal growth arrest changes starting with transverse lucent lines were demonstrated. Within a year a dense growth arrest line migrating away from the epiphysis and concomitant peripheral exostosis formation at the edge of the growth disturbance zone were seen, clearly showing that the same chronologic factor was manifest in the neoplastic as well as the dysplastic changes. Radioautographs in rabbits given thorium-X confirmed the deposition of the substance in cartilage. Two of the 3 patients died of osteogenic sarcoma; Spiess does not mention the prior existence of exostosis at the site of the sarcoma. Thorium-X, emitting beta, alpha and gamma rays in its decay scheme, was responsible for the development of benign (exostosis) and malignant (osteogenic sarcoma) changes in the same patients.

One patient, seen at Babies Hospital in 1954, had been treated elsewhere as an infant in 1949 for a large cavernous hemangioma of the right wrist. Six radon seeds had been permanently implanted, and gross ulnar destruction and radius distortion with bowing resulted (Fig. 8, A and B). A pseudo-Madelung deformity of the radius developed which proved resistant to multiple corrective procedures. If an activity of 0.5-1.0 mc per seed can be assumed, the ulna received probably more than 3,000 gamma r to its distal growth center, the radius less by virtue of the greater distance. Malignant change of a histologic nature did not develop although a great functional deformity resulted. The severe accompanying muscle wasting and fibrous contractures were felt to be the cause of the progressive bowing of the radius.

SUMMARY AND CONCLUSION

Infants and children treated by irradiation for both benign (hemangiomas) and malignant disease (Wilms' tumor, neuroblastoma, retinoblastoma) have shown radiation induced growth disturbances on serial studies. Undergrowth, vertebral distortion resembling Morquio's spondyloepiphyseal dysplasia, severe muscle and bone atrophy and malignant transformation (osteogenic sarcoma arising 10 years after treatment of a retinoblastoma) are discussed. Radiation effects were found to be related to the age of the patient, the nature of the primary disease, and the amount and quality of the radiation which was delivered.

An unusual case of unilateral hyperlucent lung in a patient cured of metastatic Wilms' tumor is presented. A proposed mechanism involving the bronchial artery-pulmonary artery shunting, and related to the metastasis, the radiation, and intercurrent pneumonia, is discussed.

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HODGKIN'S DISEASE*

A REVIEW OF RADIOTHERAPEUTIC EXPERIENCE

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IN AN entity such as Hodgkin's disease in which involvement of practically every organ and lymph node bearing area may occur, the histologic appearance may vary, and the course may be influenced by natural fluctuations and occasional long-term remissions, it is difficult to predict the result of any form of therapy. In spite of the introduction of several new chemotherapeutic agents in recent years, the most effective form of treatment of the disease still remains the judicious use of radiation therapy. General opinion today favors the use of higher doses of radiation than customary in the past,⁵ an opinion with which we agree. The material available at the University of Michigan, however, includes patients treated with low radiation doses who have been followed over the years. The occurrence of long term survivors among these prompted the study of such patients as well as others with respect to the influence of age, sex, clinical and histologic classification, as well as radiation dose, upon survival.

CLINICAL MATERIAL AND METHODS

Four hundred and ten patients with Hodgkin's disease were irradiated at the University of Michigan Medical Center from the year 1940 through 1962 (Table I). With few exceptions, treatment was started after the histologic diagnosis of Hodgkin's disease had been made by the Department of Pathology at the University of Michigan. In a few instances, therapy was initiated as a test of irradiation because a histologic diagnosis could not be established; most of these cases were confirmed by biopsy later. For the present study, the original biopsy and necropsy materials were

TABLE I

HODGKIN'S DISEASE 1940 THROUGH 1962

Patients Previously Untreated:		
Radiotherapy at University of Michigan Medical Center		288
Slides reviewed	268	
(1940 through 1955)		175
(1956 through 1962)		93
Slides not available for review	12	
Hodgkin's disease not confirmed	8	
Patients Previously Treated		122
Total		410

reviewed without reference to the clinical course of the disease.

The cases were divided in two major groups (Table I). In the first were the patients, 288 in number, who had not received any form of treatment prior to their initial treatment with radiation at the University of Michigan. The second group was composed of 122 patients who had received some form of therapy, irradiation or chemotherapy, prior to their acceptance for treatment with radiation at our institution. Because of the unreliability of determining survival time from first treatment, the difficulty in accurately staging them and of obtaining details of previous therapy, these 122 patients were eliminated from the study.

Of the 288 cases initially treated in this hospital, 1940 through 1962, the diagnosis of Hodgkin's disease was confirmed histologically by this review in 268. Of these, 175 were treated during the years 1940 through 1955 and have a follow-up period of at least 5 years. Ninety-three were

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TABLE II
CLINICAL STAGING OF HODGKIN'S DISEASE

Stage I	a. Involvement of only one lymph node region or a single extranodal lesion No constitutional symptoms b. Same as Ia, with constitutional symptoms
Stage II	a. Involvement of two or more contiguous lymph node regions confined to either upper or lower trunk Abdominal involvement Single extranodal site with involvement of adjacent lymph node region No constitutional symptoms b. Same as IIa, with constitutional symptoms
Stage III	a. Involvement of multiple lymph node regions of upper and lower trunk Systemic involvement Liver, spleen or bone marrow involved Single extranodal site plus involvement of remote lymph node region(s) Peripheral plus retroperitoneal lymphadenopathy. No constitutional symptoms b. Same as IIIa, with constitutional symptoms, includes acute Hodgkin's disease with no obvious lymph node involvement

treated during the years 1956 through 1962 and include patients receiving "prophylactic" irradiation, a practice instigated in 1956.

Of the 20 cases in which the diagnosis could not be confirmed, tissue sections for 12 were not available for review although a histologic diagnosis of Hodgkin's disease had been made in the past (5 of these patients lived 5 or more years after institution of treatment); 2 were cases of lymphoma that could not be classified; 1 was reclassified as histiocytic medullary reticulocytosis and another as a non-neoplastic process. The biopsy material was inadequate in 4.

The present study is based on the 268 patients whose *initial* treatment was irradiation at this institution and whose diagnosis of Hodgkin's disease was confirmed by the present review of the histologic slides.

Survival time was calculated from the

date of initial treatment rather than the date of onset of symptoms or time of diagnosis. Patients who died of other causes were considered as dying of Hodgkin's disease. A few patients died before completion of initial therapy and are included in the series. No patient was lost to follow-up. No correlations regarding race have been made in view of the few non-whites in the group (261 white, 6 Negro and 1 oriental).

For the study, the pertinent information obtained from each hospital record was coded and introduced into cards using an inverse grouping technique; data were retrieved by the method of optical coincidence.¹

CLINICAL CLASSIFICATION

The clinical classification into stages used in this study is the one proposed by Peters and Middlemiss,⁹ slightly modified (Table II). Each of the three stages has been divided into two substages according to the presence or absence of constitutional symptoms.

The relationship of stage to survival rate is shown in Table III. Most patients (44 per cent) were classified as Stage II; Stage III was next in frequency (38.3 per cent); and Stage I the least common (17.7 per cent). Constitutional symptoms as one would expect were more frequent in patients with more advanced involvement and had a constant adverse effect on survival in all stages. The more advanced form of the disease, Stage III, was more frequent in the older groups (Tables VI and VII).

AGE AND SEX

The age distribution by decades of the 175 patients treated from 1940 through 1955 is shown in Figure 1. The disease was most common in the group 20 to 29 years of age (21 per cent)—an observation similar to that of others.^{4,9} For each decade the sex distribution is shown in Figure 1. There were in all 114 (65.1 per cent) males and 61 (34.9 per cent) females, a proportion of almost 2 to 1 in favor of the male. This

TABLE III
RELATION OF CLINICAL CLASSIFICATION AND 5 YEAR SURVIVAL
(1940-1955)

Stage	No. of Patients	Per Cent of Entire Group	5 Year Survivors	
			No. of Patients	Per Cent
ia	24	13.7	12	50.0
ib	7	4.0	2	28.6
Stage I Total	31	17.7	14	45.2
IIa	41	23.4	19	46.3
IIb	36	20.6	14	38.9
Stage II Total	77	44.0	33	42.9
IIIa	10	5.7	2	20.0
IIIb	57	32.6	7	12.3
Stage III Total	67	38.3	9	13.4
Grand Total	175	100.00	56	32.0

proportion was essentially maintained throughout all age groups except in the third decade, where the distribution of male and female was about equal. Similar age and sex distributions were found when the

total group of 268 patients was studied; 65.3 per cent were male and 34.7 per cent female.

The 5 year survival rate for each decade is presented in Figure 2. The survival rate

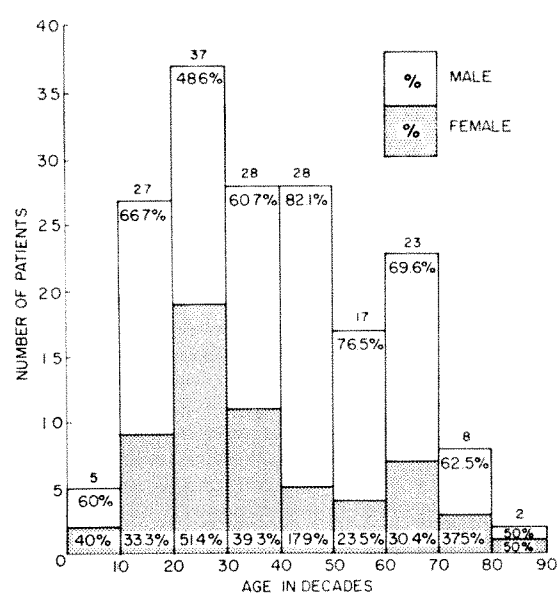


FIG. 1. Hodgkin's disease. Age and sex distribution (1940-1955).

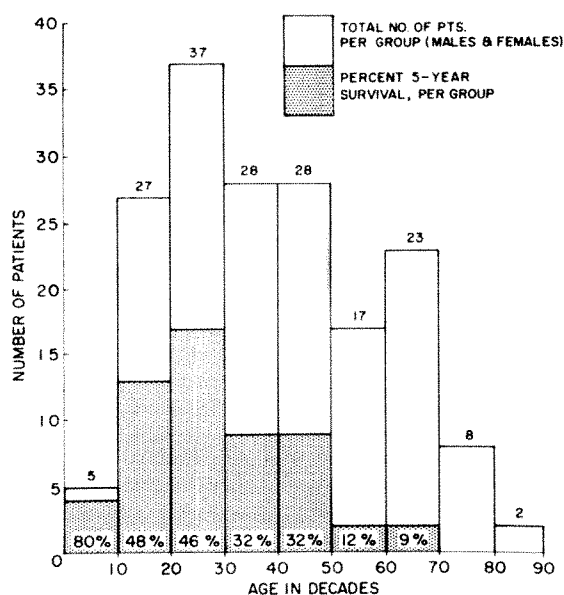


FIG. 2. Hodgkin's disease. Age at onset of disease (males and females) and 5 year survival.

is greater in the first three decades decreasing thereafter. These findings are similar to those of Peters and Middlemiss.⁹

When the male and female patients are gathered into 3 separate groups according to age of onset of the disease, 0-29 years, 30-59 years, and 60 years and over, and in each such group survival is determined, it is noted that in both sexes survival rates decrease with advancing age (Table IV).

The 5 year survival rate was 27.2 per cent for males and 41 per cent for females. This difference in survival rate suggests a better prognosis in the female but in this series the result is not statistically significant, $X^2=3.5$. Similarly, the data presented by Peters and Middlemiss⁹ are inconclusive, although the results of Jelliffe and Thomson⁴ tend to confirm this impression as they obtained a 5 year survival rate of 42 per cent for 64 females and 21 per cent for 107 males; a significant statistical difference, $X^2=8.32$.

The relation of sex to stage and age is presented in Table v. The 5 year survival rate is higher for females in Stage I, 60.0 per cent versus 38.1 per cent for males, and in Stage II, 47.2 per cent as compared to 39.0 per cent for males. When in each of these stages, the patients are subdivided into those with disease onset in the first three decades (0-29 years), and those with subsequent onset (30 years of age and over), the higher survival rates for females

are consistently maintained. With the numbers available, however, statistically significant differences cannot be demonstrated. The consistency of the phenomenon in Stage I and II and in each age subgroup is striking. Such consistent differences do not appear in Stage III, suggesting that disseminated disease wipes out a favorable sex factor.

Tables VI and VII correlate the clinical and histologic classification with age and sex. The incidence of Stages II and III is different for the two sexes. Thirty-six per cent of the males are in Stage II and 45.6 per cent in Stage III, compared to 59 per cent and 24.6 per cent respectively for the females. In each sex, the incidence of Stage II decreases with advancing age while the incidence of Stage III increases. Stage I, however, remains about the same.

Constitutional symptoms were present in about the same proportion in each sex, 42.1 per cent in the males and 44.3 per cent in the females.

The distribution of the three histologic groups is also approximately the same in the two sexes. The sarcomatous form of the disease was more common in the older age group (Tables VI and VII).

HISTOLOGIC CLASSIFICATION AND SURVIVAL

The classification of Jackson and Parker,⁸ dividing Hodgkin's disease into para-

TABLE IV
HODGKIN'S DISEASE: DISTRIBUTION BY SEX, AGE AT ONSET
OF DISEASE IN DECADES AND 5 YEAR SURVIVAL
1940-1955

Age at Onset of Disease	Males			Females		
	No. of Patients	5 Year Survivors		No. of Patients	5 Year Survivors	
		No. of Patients	Per Cent		No. of Patients	Per Cent
0-29	39	17	43.6	30	17	56.7
30-59	53	13	24.5	20	7	35.0
60-and over	22	1	4.5	11	1	9.1
Total	114	31	27.2	61	25	41.0

TABLE V
HODGKIN'S DISEASE: DISTRIBUTION BY SEX, CLINICAL CLASSIFICATION,
AGE AT ONSET OF DISEASE AND 5 YEAR SURVIVAL
1940-1955

	Males			Females		
	No. of Patients	5 Year Survival		No. of Patients	5 Year Survival	
		No. of Patients	Per Cent		No. of Patients	Per Cent
Stage I						
Age 0-29	7	4	57.1	4	4	100.0
30 and over	14	4	28.6	6	2	33.3
Total	21	8	38.1	10	6	60.0
Stage II						
Age 0-29	24	11	45.8	22	11	50.0
30 and over	17	5	29.4	14	6	42.9
Total	41	16	39.0	36	17	47.2
Stage III						
Age 0-29	8	2	25.0	4	2	50.0
30 and over	44	5	11.4	11	0	0.0
Total	52	7	13.5	15	2	13.3
Total All Stages	114	31	27.2	61	25	41.0

granulomatous, granulomatous, and sarcomatous types, was used. Some intermediate patterns were encountered, but all of these had some granulomatous features and were so classified. It is perhaps presumptuous to attempt a histologic classification of Hodg-

kin's disease on the basis of a single biopsy in a patient with extensive involvement, but no other course was open to us.

Table VIII shows the relationship between the histologic type, stage, and survival rates. The inherent uncertainty of

TABLE VI
DISTRIBUTION OF HODGKIN'S DISEASE BY SEX, AGE AT ONSET
OF DISEASE, STAGING AND HISTOLOGIC DIAGNOSIS
1940-1955
Males

Age at Onset of Disease	No. of Patients	Staging (Per Cent)			Histology (Per Cent)		
		I	II	III	Para-granuloma	Granuloma	Sarcoma
0-29	39	18	62	20	3	92	5
30-59	53	19	23	58	6	79	15
60-89	22	18	23	59	5	68	27
Total	114	18.4	36.0	45.6	4.4	81.6	14

TABLE VII
DISTRIBUTION OF HODGKIN'S DISEASE BY SEX, AGE AT ONSET OF DISEASE,
STAGING AND HISTOLOGIC DIAGNOSIS
1940-1955
Females

Age at Onset of Disease	No. of Patients	Staging (Per Cent)			Histology (Per Cent)		
		I	II	III	Para-granuloma	Granuloma	Sarcoma
0-29	30	13	74	13	—	97	3
30-59	20	15	60	25	5	90	5
60 and over	11	27	18	55	9	36	55
Total	61	16.4	59.0	24.6	3.3	83.6	13.1

TABLE VIII
5 YEAR SURVIVAL ACCORDING TO HISTOLOGIC AND CLINICAL CLASSIFICATION
(1940-1955)

Classification	No. of Patients	Per Cent of All Cases	5 Year Survivors	
			No. of Patients	Per Cent
<i>Paragranuloma</i>				
Stage Ia	1		1	100.0
IIa	1		1	100.0
IIIb	4		0	0
Total	6	3.4	2	33.3
<i>Granuloma</i>				
Stage Ia	21		11	52.4
Ib	6		2	33.3
IIa	37		17	45.9
IIb	33		14	42.4
IIIa	7		2	28.6
IIIb	41		7	17.1
Total	145	82.9	53	36.6
<i>Sarcoma</i>				
Stage Ia	2		0	0
Ib	1		0	0
IIa	3		1	33.3
IIb	3		0	0
IIIa	3		0	0
IIIb	12		0	0
Total	24	13.7	1	4.2
Grand Total	175	100.0	56	32.0

TABLE IX
RADIATION THERAPY DOSE AND 5 YEAR SURVIVAL
(1940-1955)

Stage	"400 r" Group			"2,000 r" Group		
	No. of Patients	5 Year Survivors		No. of Patients	5 Year Survivors	
		No. of Patients	Per Cent		No. of Patients	Per Cent
I	8	2	25.0	14	9	64.3
II	26	8	30.8	13	6	46.2
Subtotal	34	10	29.4	27	15	55.6
III	35	4	11.4	—	—	—
Grand Total	69	14	20.3	27	15	55.6

the histologic classification may be responsible for so many Stage IIIB cases in the paraganuloma group. The granulomatous form was most common (145 cases); the 5 year survival rate in this group was 36.6 per cent with decreasing survival in advancing stages and in patients with constitutional symptoms. Twenty-four patients had a diagnosis of Hodgkin's sarcoma; only 1 survived 5 years. Most of the patients in this group had advanced disease when first treated.

TREATMENT

The technique of radiation treatment of Hodgkin's disease used over the period under study can be grouped into three broad categories. In the early 1940's, all stages were treated with orthovoltage radiation (200 kv.) and a single regional dose of 400 r measured in air was given to the area involved. If more than one region was involved, several fields were used but each field received the same dose. Local recurrences were treated in the same way. We have called this method the "400 r" program.

In the late 1940's and early 1950's, some patients were treated with the same radiation with slightly higher doses, totaling about 1,000 r, measured in air, over a

period of 4 to 5 days. In mid 1950's an increase in the total regional dose was made. New patients were treated on a daily basis, generally with orthovoltage radiation (250 kv. constant potential, half value layer of 2.7 mm. Cu) until a dose of 2,000 r in air was given to a region in approximately 11 to 14 days. A few received higher doses and others received between 1,500 r and 2,000 r to a region. This regimen applied mainly to cases classified as Stage I or II. We have called this method the "2,000 r" program. None of the patients treated from 1940 through 1955 received "prophylactic" irradiation to regional areas not known to be affected by the disease, a practice which was started in 1956.

Chemotherapy has been used for those patients who subsequently developed generalized manifestations of the disease after initial radiation therapy. It has been of great value in ameliorating symptoms of systemic manifestations of the disease. Regression of lymphadenopathy and other masses occurred but, in general, tended to be of short duration.

RESULTS

Table IX presents the results of the lower radiation doses (the "400 r" group) used in the early years covered by this study, as

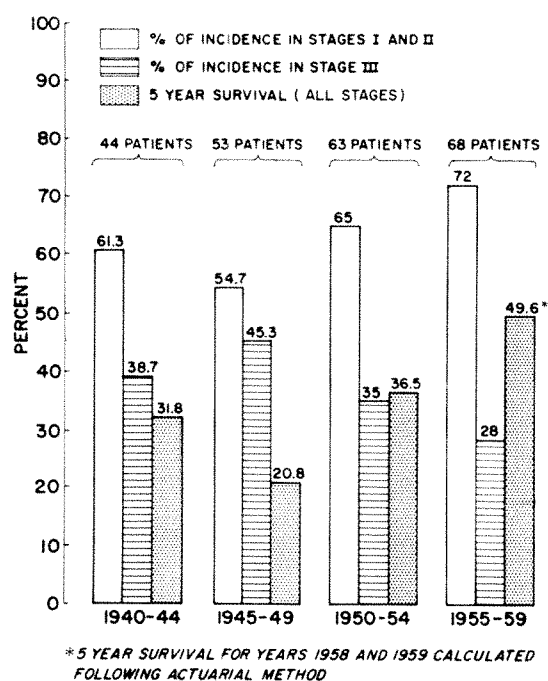


FIG. 3. Hodgkin's disease. Distribution of clinical stages and 5 year survival rate divided in 5 year periods.

compared with those of the higher doses (the "2,000 r" group). The patients treated with doses between these two groups were excluded. Of 69 patients treated in the "400 r" program, an over-all 20.3 per cent 5 year survival was found; for Stages I and II, the 5 year survival rate was 29.4 per cent.

Of 27 patients treated in the "2,000 r" program in Stages I and II, 15 (55.6 per

cent) were alive at 5 years. No Stage III case was treated by this method. The difference between 29.4 per cent and 55.6 per cent is statistically significant ($X^2=4.3$).

When the 5 year survival of the patients treated from 1940 through 1959 is analyzed in 5 year periods starting in 1940, we find (Fig. 3) a 31.8 per cent survival in the 1940 through 1944 period. Survival decreases to 20.8 per cent in the next period (1945 through 1949) and from there on increases steadily up to the 1955 through 1959 period where the predicted survival is 49.6 per cent, using the life table computation method. (The actual 5 year survival for the years 1955, 1956, and 1957 was 51.2 per cent.)

This increase in the 5 year survival rate in most recent years can be attributed to the beneficial effects of higher doses of radiation used, as attested by increased survival in Stages I and II in the 1950-1957 group when compared to the 1940-1949 period: 52.1 per cent versus 35.7 per cent (Table x). However, a part of the over-all improvement is due to a lower incidence of Stage III cases in the 1950-1957 group, 31.1 per cent compared to 42.2 per cent in the 1940-1949 group.

It is to be noted that the lowest survival rate was in the period 1945-1949, when the highest incidence of Stage III was present (Fig. 3).

Seventy patients have been followed for 15 years or longer (Fig. 4). About 50 per

TABLE X
HODGKIN'S DISEASE: DISTRIBUTION OF CLINICAL STAGE AND 5 YEAR SURVIVAL
1940-1957

Stage	1940-1949			1950-1957		
	No. of Patients	5 Year Survival		No. of Patients	5 Year Survival	
		No. of Patients	Per Cent		No. of Patients	Per Cent
Stage I and II	56	20	35.7	73	38	52.1
Stage III	41	5	12.2	33	5	15.2
Total	97	25	25.8	106	43	40.6

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HODGKIN'S DISEASE OF BONE*

FAVORABLE PROGNOSTIC SIGNIFICANCE?

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IT IS frequently stated that the most important factor in estimating prognosis in Hodgkin's disease is the clinical stage at the time of diagnosis or first treatment.² It has been our clinical impression for some years that our patients with bone lesions tolerated their disease better and survived longer than those with clinical manifestations limited to soft tissues only. Inasmuch as bone involvement almost always indicates a Stage III classification,^{4,7,10} we felt that an attempt to verify this seemingly paradoxical impression would be of interest. We, therefore, reviewed all cases of Hodgkin's disease seen at this hospital from 1946 to January, 1964, with special reference to bone lesions.

REVIEW OF LITERATURE

Diverse opinions as to the significance of the osseous lesions of Hodgkin's disease have been expressed. In a survey of the pertinent literature,^{1,3,8,9,11} we found a statement in the excellent review of Vieta *et al.*¹³ in 1942 to the effect that their patients with bone lesions seemed to have a longer survival. In contrast, Uehlinger¹² believed that bone involvement was of grave significance. Fucilla and Hamann⁶ expressed the opinion that the prognosis was not altered when such lesions were present.

In a recent lengthy review of the factors influencing prognosis,² the variables considered included: stage of the disease at onset, histologic classification, presence of constitutional symptoms, age, sex, pregnancy, and location of the primary manifestations. Such miscellaneous complications as herpes zoster and jaundice were also discussed. Interestingly, the question of bone involvement was not mentioned.

MATERIAL

It is realized that the diagnosis of Hodgkin's disease of bone is subject to a variety of interpretations. We are speaking of that bone involvement in a patient with known Hodgkin's disease which is: (1) either clinically symptomatic, thereby calling attention to its presence, or (2) so striking on roentgenograms as to be easily diagnosed. Autopsy examination will show microscopic evidence of Hodgkin's involvement of the bone marrow in virtually 100 per cent of cases regardless of clinical symptoms during life.⁵ Bone lesions were rarely biopsied inasmuch as the typical roentgenographic appearance in conjunction with the

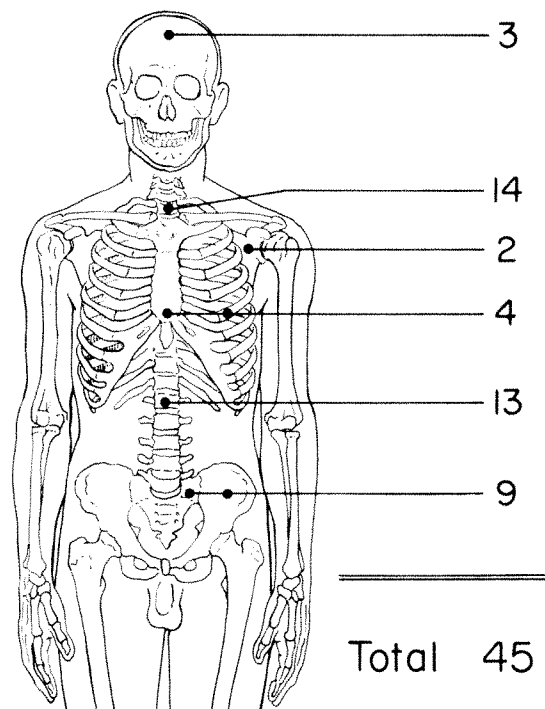


FIG. 1. Location of bone lesions in Hodgkin's disease—30 patients.

* From the Radiology Service, Therapy Section and Medical Service, Oncology Section, Veterans Administration Hospital, Long Beach, California.

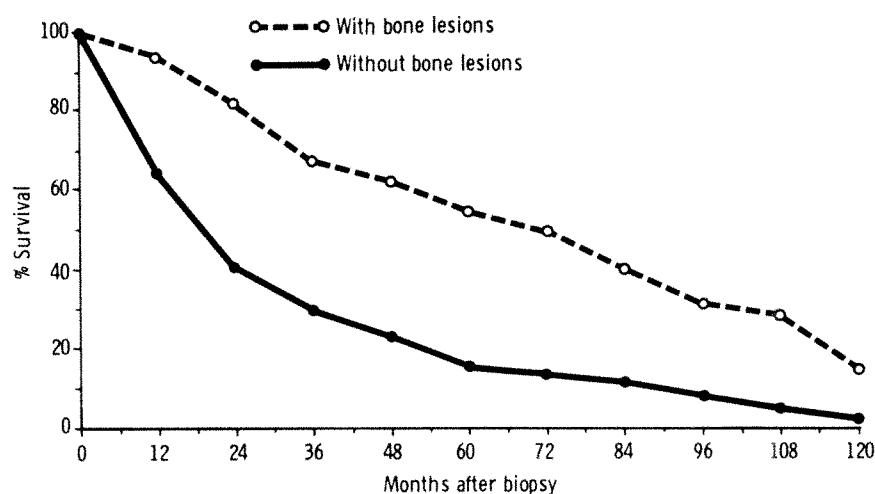


FIG. 2. Survival rate of patients with Hodgkin's disease.

soft tissue biopsy and clinical course were considered sufficient.

We reviewed 179 cases of Hodgkin's disease, all males 20 years of age or older. Of these, 158 had complete clinical records, biopsy proof, and roentgenograms available for study. Of the 158 evaluable cases, 30 had clinical bone involvement during their course for an incidence of 19 per cent. In Fucilla and Hamann's review of 5 series totaling 722 cases of Hodgkin's disease,

the average incidence of bone involvement was 15.1 per cent.

RESULTS

The question of "date of onset" of any malignant disease is subject to interpretation of definition. We used the first date of biopsy proof of Hodgkin's disease as the date from which survival was measured. The biologic onset of the disease may be months to years prior to this arbitrary

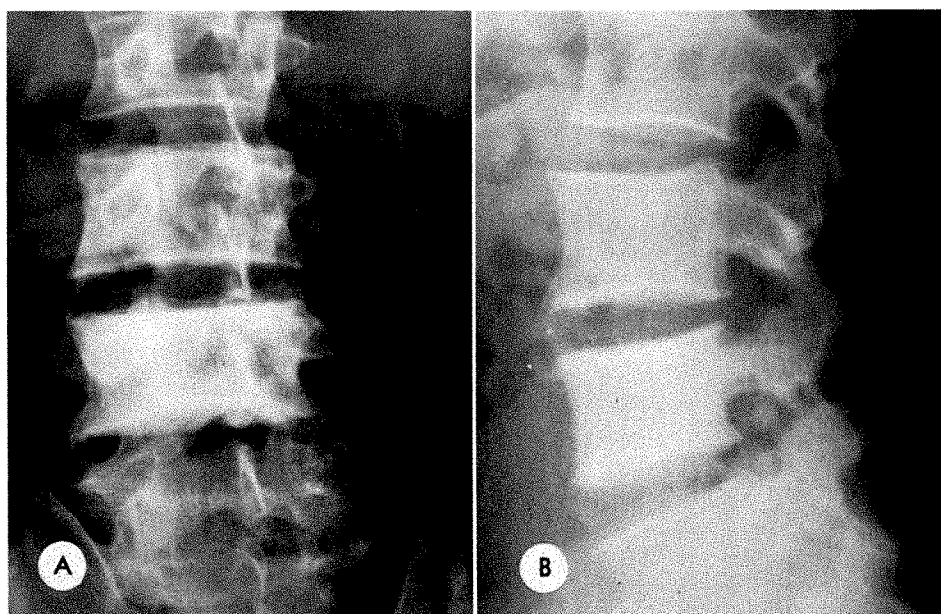


FIG. 3. (A and B) Sclerotic 4th lumbar vertebra; the most frequently seen lesion.



FIG. 4. Lytic lesion of the 3rd lumbar vertebra.

date; nevertheless, we felt this made a uniform criterion for all cases for purposes of comparison.

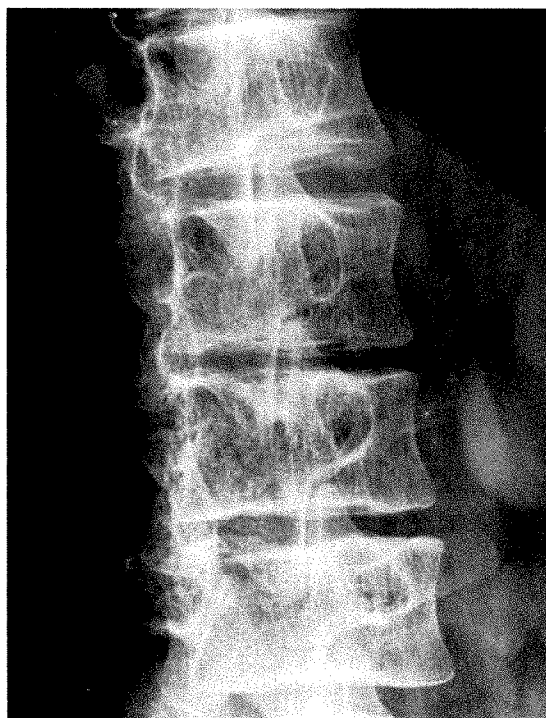


FIG. 5. Diffuse loss of fine trabeculation.

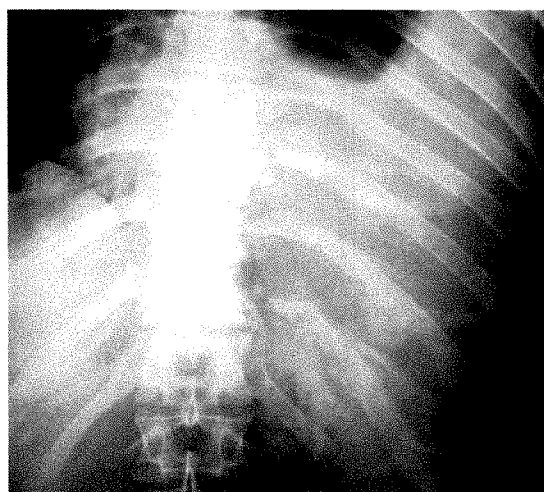


FIG. 6. Same patient as in Figure 5. Sclerosis and partial collapse of the 10th and 11th thoracic vertebrae. Destruction of several left ribs with associated pleural effusion and soft tissue masses.

In these 30 cases, there were 45 separate areas of bone involvement, each of which may have represented several bones. The thoracic and lumbar vertebrae were most frequently involved, followed less often by the pelvis and sacrum. The ribs, sternum, scapulae, and skull were each affected in a few cases. The distribution of bone involvement is seen in Figure 1. Of the 30 patients, 13 had only sclerotic lesions, 11 only lytic lesions, and 6 of them had both. Examples of bone lesions are shown in Figures 3 through 8. Local pain called attention to most of these lesions, particularly the lytic ones. Sclerotic areas were an incidental asymptomatic roentgenographic finding in

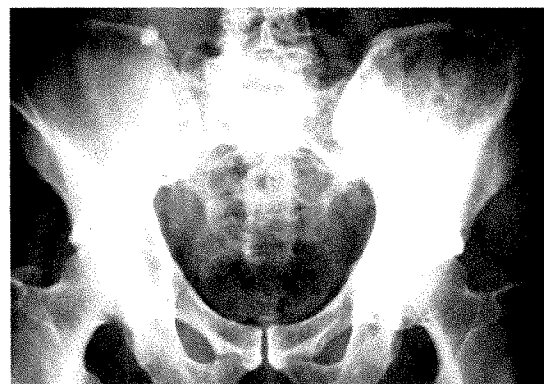


FIG. 7. Sclerosis of left innominate bone.

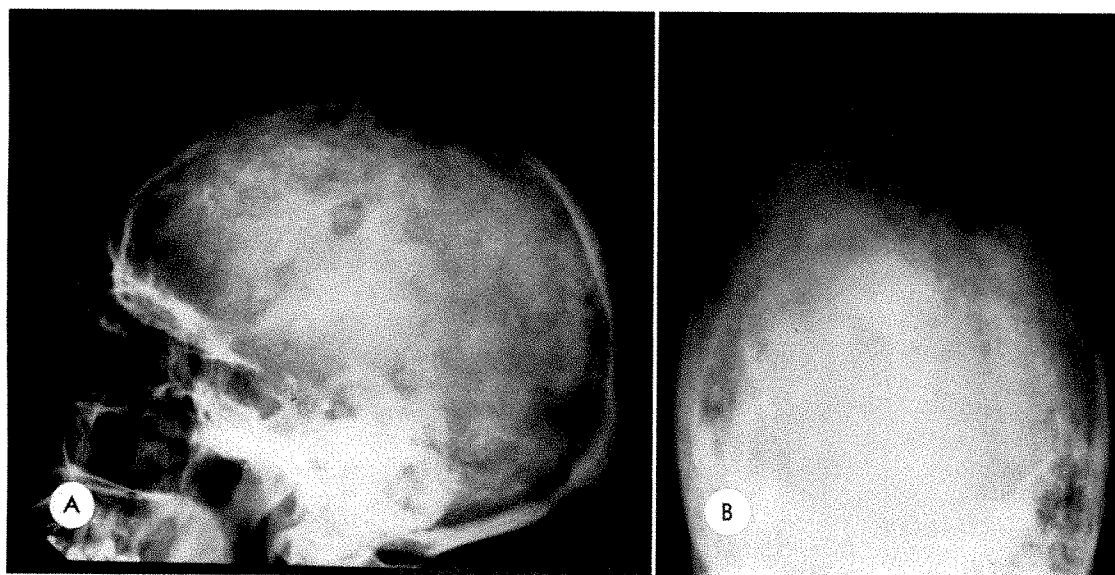


FIG. 8. (*A* and *B*) Several lytic lesions of the calvarium.

a few patients. Radiation therapy was almost always effective in controlling symptoms of bone lesions, but only a few cases showed evidence of healing on subsequent roentgenograms. Bone involvement is said to occur either by hematogenous dissemination or by direct extension of soft tissue masses. The most destructive lesions seemed to be associated with invasion from contiguous masses. Invasion of the medullary portion of bone is less easily detected on roentgenograms than is cortical destruction. The bone lesions appeared late in the course of the disease in some patients, very early in others. One patient presented initially with diffuse lytic bone lesions, and soft tissue disease did not appear until several years later.

Figure 2 shows the survival rate of patients with bone lesions as contrasted with those without such involvement. The difference in survival is already evident at the end of the first year with 93 per cent of the bone disease group alive versus 66 per cent of the soft tissue group of patients. At 5 years the figures are more striking with 57 per cent of the bone group alive as opposed to only 16 per cent of those with soft tissue disease. At 10 years, the differences are less spectacular, but still present. Of all pa-

tients surviving 10 years or more, over half showed bone involvement. In the series of Vieta and colleagues,¹³ similar differences in the survival of patients with bone disease were recorded in the first few years. However, at 5 years the survival percentages were nearly equal, and remained the same up to 7 years, the end of their observation period.

As of January, 1964, 22 of the 158 patients were alive. Thirteen of these have been followed for less than 10 years, the remaining 9 for over 10 years. It might be inferred that if patients with Hodgkin's disease live long enough, bone lesions are likely to become demonstrable. However, this did not seem to be the case. More frequently, the bone lesions appeared early in the course of those who subsequently demonstrated a prolonged survival. Of our 136 deceased patients, the average survival was 4.2 years. The average survival of patients with bone lesions was 6.5 years, as opposed to an average of 3.6 years for those with only soft tissue involvement.

SUMMARY AND CONCLUSIONS

1. Of 158 patients with Hodgkin's disease, 30, or 19 per cent showed bone involvement.

2. Unlike other forms of malignant disease involving bone, that seen in Hodgkin's disease occurs in patients who have a longer survival than patients without such clinical manifestations.

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RADICAL IRRADIATION OF ADVANCED BREAST CANCER *

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THE widespread opinion among surgeons that permanent control of breast cancer cannot be obtained by irradiation often leads to performing a radical mastectomy on patients with locally advanced tumors despite the known risk of a rapidly appearing carcinomatosis in the operative area. The justification has been that "radical mastectomy is the only chance" offered to patients for an occasional cure.

A review of the literature^{1,14} shows that if one does not use rigid criteria to select cases for operation, the incidence of local recurrence is high. With modern hormonal and chemotherapeutic management of breast cancer, internal metastases can be kept in check for lengthy periods of time. Disease recurring in the local area is seldom completely eradicated by hormonal management and patients have to live with obvious disease on the chest wall, in the axilla or supraclavicular region. This external disease may be the dominating event of the last period of their life and at times is an enormously troublesome problem of management for the families and for the physician in charge of the patient. Freedom from external disease on the chest wall and the regional lymphatic areas, therefore, is of great benefit to the patient. Hence, the analysis of the results of treatment should not only include survival rates but also freedom from local disease.

In 1943, Haagensen and Stout¹³ reviewed the course of 109 patients with breast cancer of whom the only three 5-year survivors (2.8 per cent) developed a local recurrence and distant metastases shortly after the 5-year follow-up. The incidence of recurrences within the operative area was 47.7 per cent in the 109 patients. Analysis of the clinical

features in this series of cases led Haagensen and Stout to define criteria of operability.

Baclesse^{3,4} initiated, in the 1930's, a long protracted irradiation technique which produced not only significant survival rates but also permanent control of tumors in both the breast and axilla. Lenz,¹⁵ in a small but interesting series of patients, using similar doses and treatment times, achieved a survival incidence of 30 per cent for patients at 8 to 10 years.

RADIOSENSITIVITY OF BREAST CANCER

When only 4,000 to 5,000 r were given in 4 to 6 weeks, poor local control of inoperable breast cancers was obtained.^{2,11} Residual tumor was found in all patients with advanced breast cancer irradiated preoperatively with doses of 4,500 to 5,500 r in 6 to 8 weeks.¹⁵ A 54 per cent 5-year survival rate was achieved in breast cancer patients treated by irradiation only with 5,000 r in 5 weeks.¹² The better results in Guttman's series point to the importance of the size of the tumor masses in securing permanent control, since those patients who underwent triple biopsies must not have had locally advanced disease. The number of cells to be sterilized is greater in large masses with a larger proportion of cells in a state of hypoxia or anoxia than in small tumors.

There is no experimental proof that long protraction of the treatment for breast cancer is superior to a shorter period of treatment time. However, the only series^{3,4,15} in which a significant percentage of local control and also long survivals have been obtained for patients with large inoperable masses are those in which therapy has been

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given with long protraction of treatment time. Better vascularization may develop as the treatment shrinks the large masses. There also may be a difference in the recovery factor of breast adenocarcinoma compared with squamous cell carcinoma.^{7,10}

In Table I data from the literature on the correlation of dose-time with local control of disease and survival rates are summarized.

CLINICAL MATERIAL

In 1948, a program was initiated between the Breast Service (headed by E. C. White, M.D.) and the Section of Radiotherapy in which not only the technically inoperable cases but also the cases with clinical features similar to those fulfilling Haagen-

sen and Stout's criteria of operability were treated only by radical irradiation (Table II). A simple mastectomy was done when the lesion was large and located in a pendulous breast or was ulcerated, which added technical difficulties for irradiation. Resection is not done if inflammatory changes are present. With exceptions (Fig. 1B) gross cut-through of the lesion is avoided. This approach is not to be identified with the McWhirter policy of treatment.¹⁶

IRRADIATION TECHNIQUE

Long protracted irradiation has been used for all patients with inoperable carcinomas; the exceptions are 15 patients who received 4,000 to 5,000 rads in 4 to 5 weeks. These 15 patients were either scheduled for

TABLE I
RADIOSENSITIVITY OF BREAST CANCER
Review from the Literature

Authors	Material	Dose in Time
Atkins and Horrigan ²	85% local residual disease in inoperable cancers	4,250 r in 4 wk. with 1.5 mm. Cu HVL, 5,000 r in 4 wk. with 22 mev. betatron
Baclesse ^{3,4}	Carcinoma of breast (excluding Stage I) 31% 5 yr., 15% 10 yr. Significant proportion of disappearance of local and axilla tumor	7,000 r or more in 12 to 14 wk.
Cohen ⁷	Miscellaneous (primary lymph nodes, chest wall nodules)	1,250 r single dose (recovery factor 0.34, skin reaction 0.35)*
Friedman and Pearlman ¹⁰	Recurrent skin nodules	Average lethal tumor dose 2,200 r; single dose (recovery factor 0.25)*
Griscom and Wang ¹¹	65% residual local disease in inoperable carcinomas	4,000 to 5,000 rads in 5 to 6 wk. using 250 kv.
Guttmann ¹²	Patients with positive triple biopsy: 54% alive at 5 yr.	5,000 r given in 5 wk. using 2 mev.
Lenz ¹⁵	Preoperative series of late cases: no instance of complete destruction	4,500 r given in 6 to 8 wk. at center of mass
	30% with no evidence of disease 8 to 10 yr. of a series of late cases treated by radiation only	6,000 to 8,000 r in 8 to 12 wk.
	Residual disease in 15 late cases treated by radiation only	Less than 5,500 r given

* Strandqvist recovery factors: skin erythema 0.31; skin cancer 0.22; therefore, for Cohen there is no increase of therapeutic ratio with fractionation.

TABLE II
TREATMENT CATEGORIES IN CANCER OF THE BREAST WITHOUT EVIDENCE OF DISTANT METASTASES AT THE UNIVERSITY
OF TEXAS M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

Category I		Category II		Category III		Category IV	
Clinical Features	Treatment	Clinical Features	Treatment	Clinical Features	Treatment	Clinical Features	Treatment
Primary < 5 cm. No skin disturbance. With or without small palpable axillary lymph nodes in level I-III	Radical mastectomy Primary in outer quadrants with histologically negative axillary lymph nodes— <i>no postoperative irradiation</i> Primary in inner quadrants or subareolar area and/or histologically positive axillary lymph nodes— <i>postoperative irradiation</i>	Primary > 5 cm. Limited skin edema or direct skin involvement over tumor Multiple low or mid-level axillary lymph nodes (< 2 cm.) Surgical interference (open biopsy, tumor-ectomy)	Preoperative roentgen-ray therapy. Radical mastectomy 5 wk. later	Primary < whole breast Skin fixation, edema, ulceration < 1/2 breast Satellite skin nodules in continuity with primary Pectoral muscle fixation Axillary lymph nodes multiple, high level, or semi-fixed Inflammatory changes Supraclavicular lymph nodes, small, mobile	Radical irradiation alone or preceded by simple mastectomy	Primary involves whole breast Skin fixation, ulceration over > 1/2 breast Satellite skin nodules at periphery of breast Chest wall fixation Massive fixed axillary lymph nodes Arm edema Large fixed supraclavicular lymph nodes Advanced age Poor medical condition	Palliative irradiation only

preoperative irradiation and the plan changed during treatment or the 12 to 14 week treatment time was not acceptable to them. An additional 79 patients who had either massive local disease, a poor clinical condition or were too aged, were treated palliatively.

KILOVOLTAGE TECHNIQUE (250 KV.—3 MM.
CU HALF VALUE LAYER)

Originally, the multiple fields outlined by Baclesse³ were used. However, since 1954 only 4 fields have been employed.

They are: the anterior axillary and supraclavicular, the posterior axillary and 2 tangential portals (Fig. 2, *A*, *B* and *C*).

The principle of the Baclesse technique is to avoid moist desquamation of the skin at the 6 week period in order that the 12 week treatment can be completed. With 250 kv., 3 mm. Cu half value layer, great attention must be given to developing erythema at the beginning of the fourth week. If the erythema is too brisk or if there is evidence of vesiculation of the hair follicles, treatment is discontinued for a week. Areas of

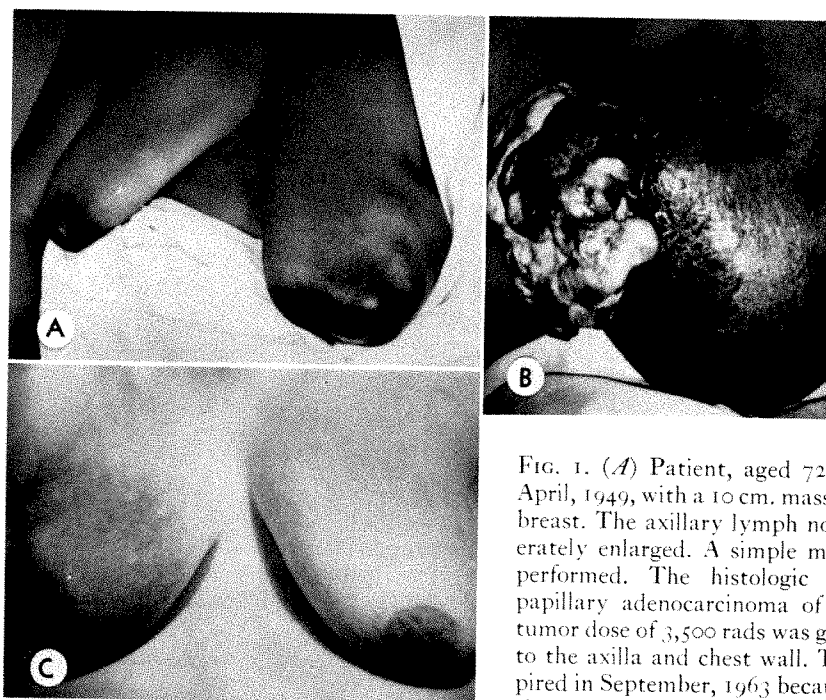


FIG. 1. (*A*) Patient, aged 72 years, seen in April, 1949, with a 10 cm. mass in a pendulous breast. The axillary lymph nodes were moderately enlarged. A simple mastectomy was performed. The histologic diagnosis was papillary adenocarcinoma of the breast. A tumor dose of 3,500 rads was given in 3 weeks to the axilla and chest wall. The patient expired in September, 1963 because of cancer of the stomach, but there was no evidence of disease from the breast tumor.

(*B*) Patient, aged 61 years, seen in January, 1951, with massive ulcerating disease of the right breast. Her hemoglobin had been reduced to 5 gm. per cent because of bleeding from the mass. No definite axillary lymph nodes were palpated. After multiple transfusions, a simple mastectomy was done for palliative purposes. The histologic diagnosis was poorly differentiated adenocarcinoma of the breast. Six weeks after the mastectomy, radical, protracted irradiation was initiated over a 12 week period. The patient was alive and clinically free from disease in December, 1964.

(*C*) Patient, aged 45 years, was seen in December, 1953, with a 10×10 cm. mass occupying the upper hemisphere of the right breast extending below the nipple and areola. The overlying skin was fixed to the entire mass and was several degrees warmer than the skin of the opposite breast. A diagnosis of inflammatory carcinoma was made clinically. An aspiration biopsy report indicated that malignant cells were present. The patient was treated from January 14, 1954 to April 15, 1954 by protracted radical irradiation given with 250 kv. The patient also underwent radiation castration. She was clinically free from disease in November, 1964, although there were severe skin and breast fibroses. Limitation of motion of the shoulder is minimal. (From Fletcher, G. H., and White, E. C. Possibilities of supervoltage roentgenotherapy in the management of cancer of the breast. *South M. J.*, 1959, 52, 805-812. Courtesy of Southern Medical Association, Publisher.)

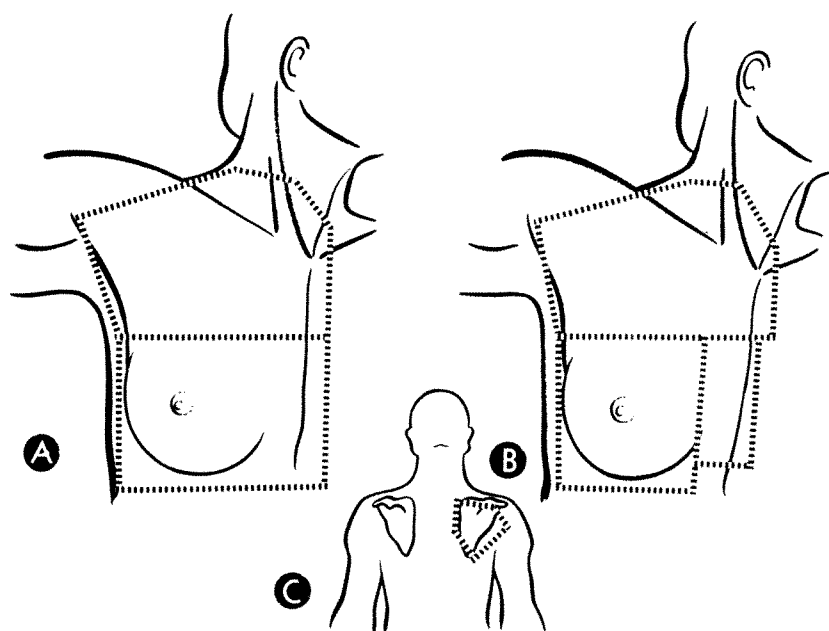


FIG. 2. (A) Tangential fields, separation 18 cm. or less.

(B) Tangential fields, separation is greater than 18 cm.; therefore, a direct internal mammary chain field is used.

(C) Posterior axillary portal. With the use of an internal mammary chain field, the 2 tangential portals are parallel; if there is no separate internal mammary chain field, the medial portal is tilted 10 degrees downward in order to assure coverage of the internal mammary chain lymph nodes.

Doses: For protracted irradiation cobalt 60 is used
Anterior supraclavicular field
Tangential fields

5,000 rads given dose in 5 weeks
q.s. for 6,000 rads tumor dose in 8 weeks
(average)

Axillary tumor dose using posterior axillary
field to bring midline axillary dose to

q.s. for 5,000 rads tumor dose in 5 weeks
(2,000 to 2,500 rads given dose)

Internal mammary chain

q.s. for 4,500 to 5,000 rads tumor dose in
4 weeks (Co^{60} 5,000 rads given dose,
 Cs^{137} 6,000 rads given dose)

moist desquamation are usually present at 5 weeks in the arm pit and inframammary fold.

The anterior and posterior axillary portals are given 400 rads (skin dose) per week; they are irradiated on alternate days twice a week, no treatment being given on Wednesday. Between 350 to 400 rads (air dose) are given per week to the tangential portals depending upon the separation of the portals. Because of the irregularity of the contour and the elongation of the tangential portals, the actual skin dose is closer to the air dose than is the skin dose obtained from the back scatter tables. If there

is too great a separation of the tangential fields, the internal mammary chain is treated separately (Fig. 2, A, B and C).

At the end of 12 weeks, the delivered skin dose to the anterior and posterior axillary portals is 4,800 rads; this produces a midaxillary tumor dose of 7,000 rads for axillae of medium size and 6,000 rads tumor dose for thicker axillae. Each tangential field receives, at the most, 4,800 rads air dose which results in an estimated tumor dose to the primary lesion in the corpus mammae of 5,000 to 6,000 rads, as the midline contribution from both tangential fields is approximately 110 to 120 per cent.

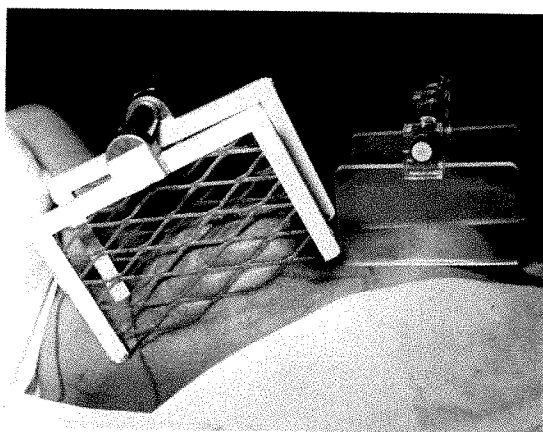


FIG. 3. Compression bridges for delivery of additional irradiation to reduced tissue volume. The plastic bridge is used to achieve maximum build-up on the skin if the skin is grossly involved.

A tumor dose of 6,000 rads is delivered to the breast by means of tangential fields. Additional treatment is delivered with fields reduced to cover only the residual tumor. The dose depends on the amount of disease present. An average of 2,000 to 3,000 rads midline bridge dose is delivered in 2 to 3 weeks.

Unless the palpable tumor in the corpus mammae and/or axilla has completely disappeared 2 or 3 weeks before completion of treatment, additional irradiation is given to the residual masses. Prior to the availability of megavoltage therapy, skin doses of 1,500 to 2,500 rads were given with the 250 kv. unit in 10 to 15 days with appositional fields covering economically residual masses. Since 1954, tumor doses of 1,500 to 2,500 rads have been given in 5 to 10 days with either a cobalt 60 unit or a short SSD cesium 137 unit with straight-on portals for irradiating the axilla or the breast, or with a small breast bridge for the tumor in the breast. Alternately, or in addition to the external beam boost, 2,000 to 4,000 rads in 2 to 4 days have been given with interstitial radium implants.

COBALT 60 TECHNIQUE

Since 1954 the long protracted irradiation has been done more and more with cobalt 60. Because there is a high probability of malignant cells infesting the dermal lymphatics in advanced tumors of the breast, a

brisk erythema is desirable even though patches of moist desquamation cannot be avoided in the inframammary fold and armpit. Bolus is used on alternate treatments to the tangential fields (Fig. 4, *A* and *B*).

A contour of the breast is made to calculate isodose distribution with bolus and without bolus (Fig. 4, *A* and *B*). In 8 weeks 6,000 rads are delivered through the tangential fields (750 rads per week) as a basic tumor dose. The skin reaction at the end of the fourth or fifth week determines the advisability of continuing using bolus. Moist

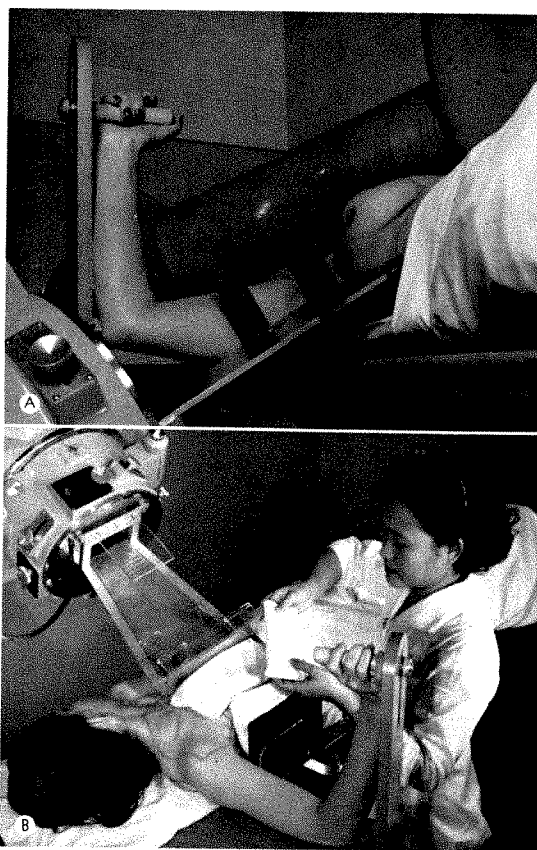


FIG. 4. (*A*) Patient in lateral tangential treatment position with breast applicator using no bolus.

(*B*) Patient in medial tangential treatment position with breast applicator using bolus.

Bolus is used on alternate treatments. In heavy, large, or pendulous breasts, the use of bolus is omitted for treatment given in the fourth and fifth weeks and use of it is resumed for treatment given in the sixth week through completion of therapy.

desquamation can be avoided by omitting bolus in the fourth or fifth week. A given dose of 5,000 rads in 5 weeks is delivered to the anterior axillary portal and q.s. to the posterior axillary portal to deliver 5,000 rads tumor dose to the midaxilla in 5 weeks. At 3 cm. depth, the internal mammary chain receives 4,500 to 5,000 rads.

Upon completion of the basic 6,000 rads tumor dose, additional irradiation to palpable residual disease in the breast and axilla is delivered by means of: (1) cobalt 60 tangential compression technique (Fig. 5), (2) interstitial radium, and (3) gold seeds, or iridium implants.

Depending upon the size of the residual masses and the technique used, 2,000 to 3,000 rads are given in 2 to 3 weeks. Occasionally, the 6,000 rads basic tumor dose has been supplemented by giving an additional 2,000 to 3,000 rads tumor dose with external beam through reduced fields (usually by the tangential compression technique) plus an extra 2,000 to 4,000 rads via interstitial radium, gold, or iridium implant. Of 14 patients so treated, with tumor doses in excess of 10,000 rads, only 2 developed major necroses. A review of the records of these 2 patients showed that the interstitial implant covered a large volume of tissue. When the volumes supplemented with both external and interstitial irradiation have been kept small, no difficulty has been noted.

IRRADIATION PRECEDED BY SIMPLE MASTECTOMY

KILOVOLTAGE TECHNIQUE (250 KV.—3 MM. CU HALF VALUE LAYER)

When the simple mastectomy scar was longitudinal, the 12 week irradiation technique has, as a rule, been used. When the scar was transverse, a skin dose of 4,000 rads was given in 4 weeks to the anterior and posterior axillary portals: an air dose of 1,000 rads in 3 weeks was given to each tangential field and an extra 1,000 rads in air in one week were given to a narrow strip covering the mastectomy scar. There were many deviations in the technique, *i.e.*, use

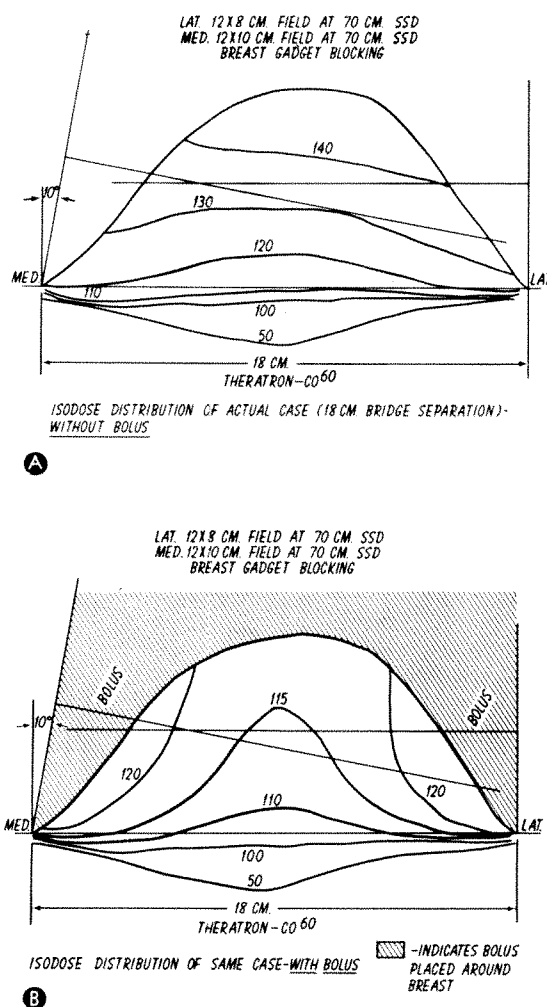


FIG. 5. (A) The dose varies from 100 per cent to 140 per cent. An average dose of 130 per cent is generally used.

(B) The tumor dose generally ranges from 100 per cent to 120 per cent with an average of 110 per cent.

of radium implants to chest wall and axilla. With this technique severe moist desquamation develops over the irradiated areas, taking weeks and at times months to heal.

COBALT 60 TECHNIQUE

With cobalt 60, the tangential fields are alternated with bolus and without bolus to deliver a tumor dose of 5,000 rads in 5 weeks. The anterior axilla-supraclavicular field receives 5,000 rads given dose, the posterior axillary field q.s. for 5,000 rads

tumor dose at midaxilla and the internal mammary field 4,500 to 5,000 rads at 3 cm. depth.

At the completion of treatment, if axillary lymph nodes are still palpable, an additional 1,000 to 2,000 rads given dose is delivered in 5 to 10 days through small portals covering the lymph nodes only. If residual induration is palpable under the scar, 1,000 rads given dose in 5 days are delivered through reduced tangential narrow fields covering the transverse scar.

In the patients with longitudinal scars, small straight-on portals with low voltage or interstitial implants (2,000 to 3,000 rads) are used to supplement the dose along the scar. Healing complications have been encountered when it was necessary to cover excessively long or irregular scars. This has been true particularly with large supplemental interstitial implants. Some patients developed prolonged moist desquamation and even chest wall necroses. In order to reduce complications, full coverage of scars

is sometimes compromised with limited volume implants or doses are reduced.

ANALYSIS OF THE RESULTS

Patient records have been coded for analysis on IBM sorting machines. Table III shows the incidence of active disease within local and regional areas for the various treatment subgroups. By order of frequency, the chest wall is the most common site of recurrent disease, then the axilla and supraclavicular areas. Parasternal nodules are the exception.

There were 47 inflammatory carcinomas in the 273 patients of the long protracted irradiation technique series. In the inflammatory cases, the local failure rate was 40 per cent, while in the noninflammatory cases the failure rate was 25 per cent. The inflammatory carcinomas were large tumors (30/47 > 7 cm.; 20/47 > 10 cm.). It is common experience that the inflammatory cases do poorly.¹⁷

The tumors in the 15 patients who re-

TABLE III
RADICAL IRRADIATION GROUPS
Incidence and Anatomic Distribution of Local Recurrences

Location of Recurrence	Protracted Baclesse Irradiation*		Total	Five Week Treatment Time	Radical Irradiation Preceded by Simple Mastectomy
	Inflammatory	Noninflammatory			
Chest wall	10	33	43	5	17
Chest wall and axilla	3	9	12	2	7
Chest wall and supraclavicular region	1	2	3	1	2
Chest wall and parasternal nodules		2	2*		
Chest wall, axilla, and supraclavicular region	1	2	3		2
Supraclavicular region	0	0	0		4
Axilla and supraclavicular region	1	0	1		5
Axilla	3	10	13	1	10
Parasternal nodules	0	0	0		
Total	19/47 (40.5%)	58/226 (25.5%)	77/273 (28%)	9/15 (60%)	47/167 (28%)

* One patient whole breast; one patient outer quadrant.

TABLE IV

PROTRACTED RADICAL IRRADIATION

Correlation of Palpable Lymph Nodes with Residual or Recurrent Disease in Lymph Node Areas

Lymph Nodes	No. of Patients	Recurrence
Axillary lymph nodes		
not palpable	42/273 (15%)	1/42 (2.4%)
single	39/273 (14%)	5/39 (12.8%)
multiple	192/273 (71%)	24/192 (12.5%)
Supraclavicular lymph nodes		*
not palpable	231/273 (85%)	6/231 (2.6%)
palpable	42/273 (15%)	1/42 (2.4%)

* All supraclavicular recurrences were associated with disease in the axilla or on the chest wall.

ceived rapid irradiation (4 to 5 weeks) did not differ materially from the remainder of the tumors in the 273 patients who had the long protracted treatment in terms of size of the primary lesion, status of the axillary lymph nodes, supraclavicular lymph nodes, and percentage of inflammatory carcinomas. Nine local recurrences in these 15 patients is in keeping with the percentage of local failures experienced in other series with similar techniques.^{2,11}

In the long protracted irradiation group an increasing incidence of failure to control disease in the breast was demonstrated in those patients who had large tumors. In

159 patients with tumors of 7 cm. or more in diameter, there were 44 (28 per cent) local failures as compared to 19 local failures in 114 patients (17 per cent) who had tumors less than 7 cm. in diameter. No difference was found in the response of inflammatory tumors for the same size and same doses. No obvious correlation could be made between tumor dose and control of tumors in the breast, because larger "boosts" were given for larger tumors.

Of the local recurrences, 75 per cent appeared within 2 years. No local recurrence has been observed after 5 years in the long protracted irradiation series; 6 local recur-

TABLE V

SURVIVAL RATES OF PATIENTS WITH BREAST CARCINOMA PREVIOUSLY UNTREATED AND WITH NO EVIDENCE OF DISTANT METASTASES AT INITIAL EXAMINATION AT THE UNIVERSITY OF TEXAS M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

January, 1948 through August, 1962

Modality	No. of Patients	Survived 3 Years	Survived 5 Years*
Radical mastectomy†	788	78.9%	66.8%
Radical irradiation§	455	45.6%	32.6%‡
{ alone	288	40.4%	27.1%
{ preceded by simple mastectomy	167	53.3%	39.8%
Total (definitive treatment)	1,243	66.8%	54.5%
Palliative treatment**	79	23.3%	8.0%
Total	1,322	64.2%	51.6%

* Berkson-Gage.

** 53% older than 70 years.

† 59% operability.

‡ In absolute number, 116 patients are alive at 5 years, 17 with disease.

§ 38% Negroes or Latin-Americans, 16% older than 70 years.

TABLE VI
WORLD RESULTS, BREAST CANCER THERAPY[§]

Authors and Years in Which Patients First Seen	Location	No. of Patients	Per Cent of Early Cases	Absolute Five Year Survival Rate (per cent)	System of Staging
Haagensen (1935-42)	Presbyterian, New York City	668	78	48	Criteria of operability
McWhirter (1941-47)	Royal Infirmary, Edinburgh	1,882	56	42	Manchester
Paterson (1940-44)	Christie, Manchester	1,675	53	29	Manchester
Smithers (1937-44)	Royal Cancer, London	1,093	57	35	Manchester
Taylor (1936-42)	Massachusetts General Hospital, Boston	430	100	56†	Criteria after Haagensen
Prudente (1939-45)	São Paulo, Brazil	64	100	57†	Criteria after Haagensen
Richards (1933-43)	Toronto General, Toronto	1,056	70	42	Richards
Robbins (1924-49)	Temple, Philadelphia	317	30	25	Portmann
Watson (1944-49)	Saskatoon, Canada	629	76	48	Manchester
Bryant (1936-47)	Ann Arbor, Michigan	742	59	40	Criteria after Haagensen
Harrington (1910-42)	Mayo Clinic, Rochester	9,649	85*	53†	Scandinavian
Nohrman (1936-41)	Radiumhemmet, Stockholm	1,042	67*	40	Scandinavian
Kaae (1931-44)	Radium Centre, Copenhagen	1,412	65*	38	Scandinavian
Adair (1935-42)	Memorial, New York City	3,836	56*	35†	
Englestad (1932-42)	Norwegian Radium, Oslo	1,384	56	40	Scandinavian

* Values adjusted from published data.

† Selected 5 year survival. Only the operated cases are reported.

‡ Published data adjusted to include all untreated cases and to assume all deaths due to breast cancer.

§ From Benninghoff, D., and Tsien, K. C.: Treatment and survival in breast cancer: A review of results. *Brit. J. Radiol.*, 1959, 32, 450-454. Courtesy of British Institute of Radiology.

rences were observed in the simple mastectomy group. No patient who developed a local recurrence within 5 years was alive at 5 years.

TABLE VII
SURVIVAL RATES IN PROTRACTED RADICAL
IRRADIATION GROUP
(Berkson-Gage)
273 Patients

Survival	No. of Patients	3 Years	5 Years
Inflammatory	47	18.0%	12.0%
Noninflammatory	226	42.9%	27.6%
Without local recurrence	196	44.0%	32.0%
With local recurrence	77	27.8%	12.6%
Palpable supraclavicular lymph nodes (absolute numbers)		10/31 (31%)	5/21 (24%)

Table IV shows a correlation between control of disease in the axilla and supraclavicular area with originally palpable lymph nodes. When lymph nodes were not palpable, either in the axilla or the supraclavicular area, failure in those sites has been exceptional. When lymph nodes were palpable in the axilla, only 12 per cent failures were experienced.

Table V shows survival rates for all patients in our series seen without evidence of distant metastases on initial examination. They compare favorably with world results (Table VI).⁵ In Table VII, survival rates of the patients with long protracted irradiation are correlated with inflammatory changes and local recurrences. The number of patients alive at 5 years with palpable supraclavicular lymph nodes points out the fact that not all patients with this unfavorable sign are dead at 5 years.

TABLE VIII

COMPLICATIONS IN PATIENTS HAVING HAD IRRADIATION ALONE OR PRECEDED BY SIMPLE MASTECTOMY

	Protracted		Five Weeks 250 kv.	Preceded by Simple Mastectomy	
	250 kv.	Co ⁶⁰		250 kv.	Co ⁶⁰
No. of cases	182	91	15	126	41
Chest wall necrosis with or without rib fracture	29 (16%)	5 (5.5%)	—	14 (11%)	2 (5%)
Minor pneumonitis and/or lung fibrosis, asymptomatic	22 (12%)	16 (18%)	1 (7%)	38 (30%)	11 (27%)
Major pneumonitis requiring treatment and/or symptomatic fibrosis	15 (8%)	3 (3%)	—	6 (5%)	2 (5%)
Axillary fibrosis	8 (4%)	1 (1%)	—	2 (2%)	4 (10%)
Frozen shoulder	2 (1%)	1 (1%)	—	—	—
Arm edema	1 (.5%)	—	1 (7%)	2 (2%)	1 (2%)
Severe skin fibrosis	5 (3%)	3 (3%)	—	3 (3%)	3 (7%)

In some patients, palpable masses in the breast or axilla are probably caused by active disease but masses can be asymptomatic and be no problem in the over-all management of generalized disease. Furthermore, a palpable mass, static and asymptomatic, does not necessarily mean active disease. For instance, a patient was submitted to a radical mastectomy for a large persistent mass in the breast; the mass was made of amorphous hyaline material.

Further irradiation was given locally in 27 of the 133 patients with local recurring disease. In 17 of the 27 patients, 4,000 to 7,000 rads (4,000 to 5,000 rads usually) in 3 to 7 days were given with interstitial γ -ray implants. There were 4 instances of necroses in that group of 17 patients. For the remaining 10 patients, external beam (140 kv., 250 kv., Cs¹³⁷, Co⁶⁰) was used. With a 22 SSD cesium 137 unit, 6,000 to 7,000 rads

were given in 3 weeks. With 140 kv. or 250 kv., 3,000 to 4,000 rads only were given in 3 weeks. No necrosis developed in this group. Control of local disease was achieved in approximately three-fourths of these patients.

Table VIII shows that severe complications are fewer in the cobalt 60 treated patients than in those treated by 250 kv. Also, late skin changes and fibrosis are less with cobalt 60. In the last few years, physiotherapy in conjunction with the beginning radiation treatment has been routine. It has diminished the incidence and severity of limitation of motion of the shoulder.

CONCLUSIONS

Bloom *et al.*⁶ have reviewed the literature on the survival rates of patients with untreated breast cancer. From the onset of symptoms (not from the onset of diagnosis) 5 year survival rates are 16 per cent in one series, 18 per cent in two series, and 22 per

TABLE IX

DIMINUTION OF LOCAL RECURRENCES IN PATIENTS HAVING HAD DEFINITIVE THERAPY FOR BREAST CARCINOMA FROM 1948 TO SEPTEMBER, 1962

	Radical Mastectomy Groups	Radical Irradiation	Total
1948-1952	28/133 (20.0%)	23/57 (40.0%)	51/190 (26.8%)
1953-1957	29/293 (10.0%)	57/167 (34.0%)	86/460 (18.7%)
1958-1962*	13/362 (3.5%)	53/231 (23.0%)	66/593 (11.1%)

* Analysis in September, 1964, 3 of local recurrences appear within 2 years.

cent in one series. Only 2.8 per cent of the 109 patients whose review led to establishment of the criteria of operability of Haagensen and Stout¹³ were alive at 5 years. In Watson's¹⁸ inoperable group (group 3) 19.9 per cent were alive at 5 years from the time of treatment. The survival rates obtained in our series are not due only to the naturally slow evolution of breast cancer. Furthermore, 99 patients (20 per cent) are clinically free from disease at 5 years or more. A significant number of patients is approaching or has passed the 10 year mark. One can state that radical irradiation can control permanently breast cancers.

Table ix shows a diminution of local recurrences through the years as the criteria shown in Table ii were applied more rigidly to the patients in our series. The survival rates and diminished incidence of local recurrences justify surgical conservatism and support the soundness of Haagensen's criteria of operability.

The ultraprotracted irradiation technique of Baclesse is an effective means of obtaining a high percentage of permanent controls of inoperable breast cancers.

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RAPID RADIOTHERAPY FOR INOPERABLE CARCINOMA OF THE BREAST*

BENEFITS AND COMPLICATIONS

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INOPERABLE carcinoma of the breast continues to be a problem of management. While hormonal therapy⁴ and other chemotherapeutic approaches have shown usefulness, radiotherapy can aid these patients by controlling the primary lesion, thus offering significant palliation. To be practical, palliative measures should be economically sound, rapidly performed, without serious sequelae and have a high degree of success.

Since 1957, a method of rapid radiotherapy for carcinoma of the breast has been employed at the Edward Mallinckrodt Institute of Radiology and has been the subject of a preliminary report.⁵ The current report is a presentation of the results in the patients treated with this technique during the initial 6 years.

METHODS AND MATERIALS

From January 1, 1957 to January 1, 1963, 47 patients with inoperable carcinoma of the breast were treated with rapid radiotherapy. The breast and lymph node bearing areas were treated with an Allis-Chalmers betatron unit producing 22.5 mev. (maximum) roentgen rays (Fig. 1, *A* and *B*). The breast or chest wall was irradiated using opposing medial and lateral tangential portals, 13 to 15 cm. in size. The lymph node bearing area on the homolateral side (including axilla, supraclavicular, and infraclavicular areas) was treated with opposing anterior and posterior portals measuring 10×10 cm. to 15×15 cm., placed so that the inferior limit of the anterior portal conformed to the upper margin of the tangential breast portals.

After the initial 18 months, the posterior portal was eliminated, since the lymph nodes are located more anteriorly. Beginning in 1961, lead blocks, 7.5 cm. thick, were placed over the superolateral aspect of the anterior portal in an attempt to decrease the incidence of "frozen shoulder" (Fig. 2, *A* and *B*). Approximately 2 cm. of underlying lung tissue was included on the tangential ports to ensure that the entire tumor volume was irradiated. Two centimeters of beeswax was used as bolus material on the anterior (lymph node) port and the tangential (breast) portals. The level of the maximum electron density (level of electronic equilibrium) was thus brought from 4 cm. below the surface to 2 cm. below the surface. Using bolus, the dose at the skin surface is estimated to be 90 per cent of the maximum dose on the anterior port and higher than this on the opposing breast portals. Because of the high energy and the bolus material, the inhomogeneity of dose is estimated to be less than 15 per cent except at the junction of the anterior and tangential fields. This area may be high or low in dosage due to either overlap or separation at this junction. Since each of these is known to occur, we now use a step field arrangement to prevent this error.

In all cases, the entire treatment to the breast was given in 2 consecutive days, followed by irradiation of the lymph node areas on the succeeding 2 consecutive days. Initially, the total tumor doses to the breast and to the lymph node areas were in the range of 1,250 r. After the early cases, the dose was increased to an aver-

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age of 2,500 r tumor dose for each area.

Table I shows the distribution of the patients and the areas to which rapid radiotherapy was applied. In this series, 76.5 per cent were advanced cases of carcinoma (Stage III or IV according to the International Clinical Staging¹¹) and 51 per cent of the patients had distant metastatic carcinoma when first seen. In 72 per cent of the patients radiation was delivered to the breast and lymph node areas as previously outlined, while in 28 per cent smaller volumes were treated. Concurrent methods of treatment were used for many of the patients. These consisted of systemic hormonal agents, systemic chemotherapeutic agents, roentgenologic or surgical castration, adrenalectomy and hypophysectomy. Eleven of the patients (23 per cent) had either a simple or radical mastectomy prior to radiotherapy. The follow-up course of all 47 patients is known. Six patients are alive with no evidence of carcinoma 59 to

68 months after treatment. Two patients survive with distant metastases 17 and 31 months after therapy. Thirty-nine patients succumbed to distant metastases; 33 of these were closely followed, while in the remaining 6 the dates of death and cause are unknown.

RESULTS

A. LOCAL CONTROL OF CARCINOMA

Follow-up data were sufficient to assess the local control of the carcinomas treated with rapid radiotherapy in 42 patients; these are presented in Table II. Correlation between the clinical control of the carcinomas and the histologic material has not been attempted. Good control is defined as permanent improvement, manifest by decrease in inflammatory elements, healing of ulcerations, decrease in size of tumor mass and alleviation of pain or other local symptoms (Fig. 3 through 6, inclusive). Thirty-seven patients fell into this category. In 2

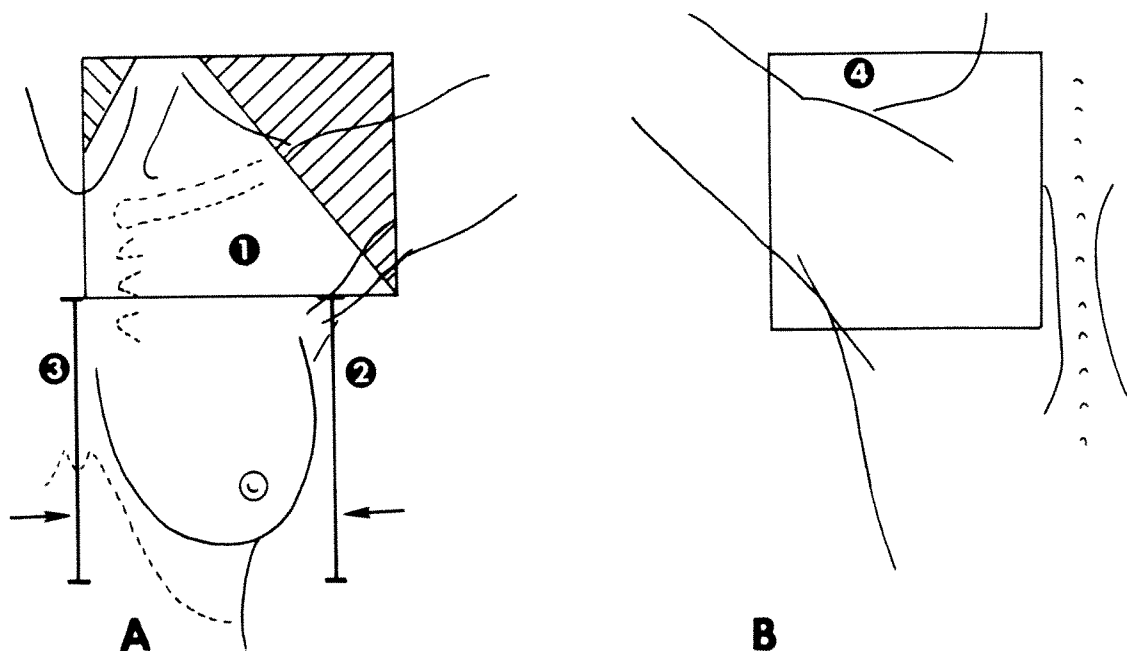


FIG. 1. (A) Anterior portal (1) for irradiation of the axillary, supraclavicular and infraclavicular lymph node bearing area and the superior portion of the anterior chest wall. Two centimeters of beeswax as bolus material is used. The shaded areas represent 7.5 cm. thick lead blocks used since 1961 to shield the superolateral portion of the shoulder and portions of the laryngopharynx. (2) Lateral and (3) medial tangential portals for treating the breast or chest wall and the lower axillary lymph nodes using 2 cm. beeswax bolus. (B) Posterior portal for treating the axillary, supraclavicular and infraclavicular lymph node bearing areas. This portal has not been used since 1959 because the lymph nodes are predominantly anterior structures.

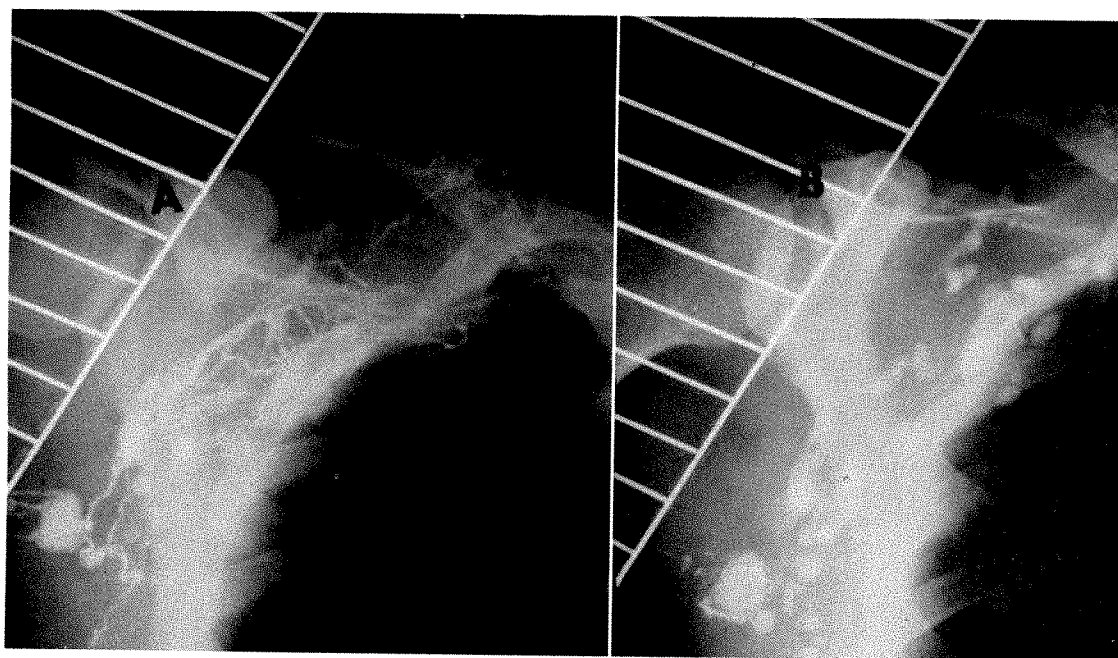


FIG. 2. Axillary lymphograms demonstrating the position of lymphatic channels (*A*) and lymph nodes (*B*) in relation to the shoulder joint. Lymph nodes are present overlying the apex of the lung and there is a lack of lymphatic tissue in the superolateral aspect of the shoulder. The shaded portions represent the areas shielded from irradiation by 7.5 cm. thick lead blocks.

patients partial control of the neoplasms was obtained (incomplete healing of ulceration, partial resolution of tumor masses and reduction of inflammatory elements or local symptoms). Both of these patients were treated for Stage IV carcinomas and both succumbed to widespread metastatic disease, 7 and 32 months after completion of rapid radiotherapy. In 3 patients there was temporary or no control of the carcinomas. Of these patients, 1 had a Stage III carcinoma (survival 7 months after radiotherapy), 1 had a supraclavicular lymph node recurrence following radical mastectomy for a Stage I carcinoma (53 month survival after radiotherapy), and the other was a Stage I patient treated immediately postoperatively following a simple mastectomy in which tumor was incompletely excised (39 month survival after completion of radiotherapy).

B. SURVIVAL

Of the 9 patients originally classified in Stage I, 5 survived an average of 62.4 months after radiotherapy without evi-

dence of persistent carcinoma (Table III), even though 2 of these survivors were treated with rapid radiotherapy for local recurrences (skin or lymph node). Two patients in Stage I had good control of the local lesions before succumbing to metastatic disease, 5 and 45 months after completion of radiotherapy. The other 2 patients in Stage I had temporary or no control of their local disease before succumbing to carcinomatosis, 39 and 53 months following radiotherapy.

The patients classified as Stage II survived 40 and 41 months with permanent local control of disease after receiving rapid radiotherapy; evidence of metastatic carcinoma was present at the time of death.

One patient with Stage III carcinoma of the breast is alive with good control of the breast and lymph node involvement but with evidence of metastatic carcinoma 31 months following rapid radiotherapy. All other Stage III patients had metastases at the time of death after surviving an average of 18 months following radiotherapy. In all of these patients good control of the pri-

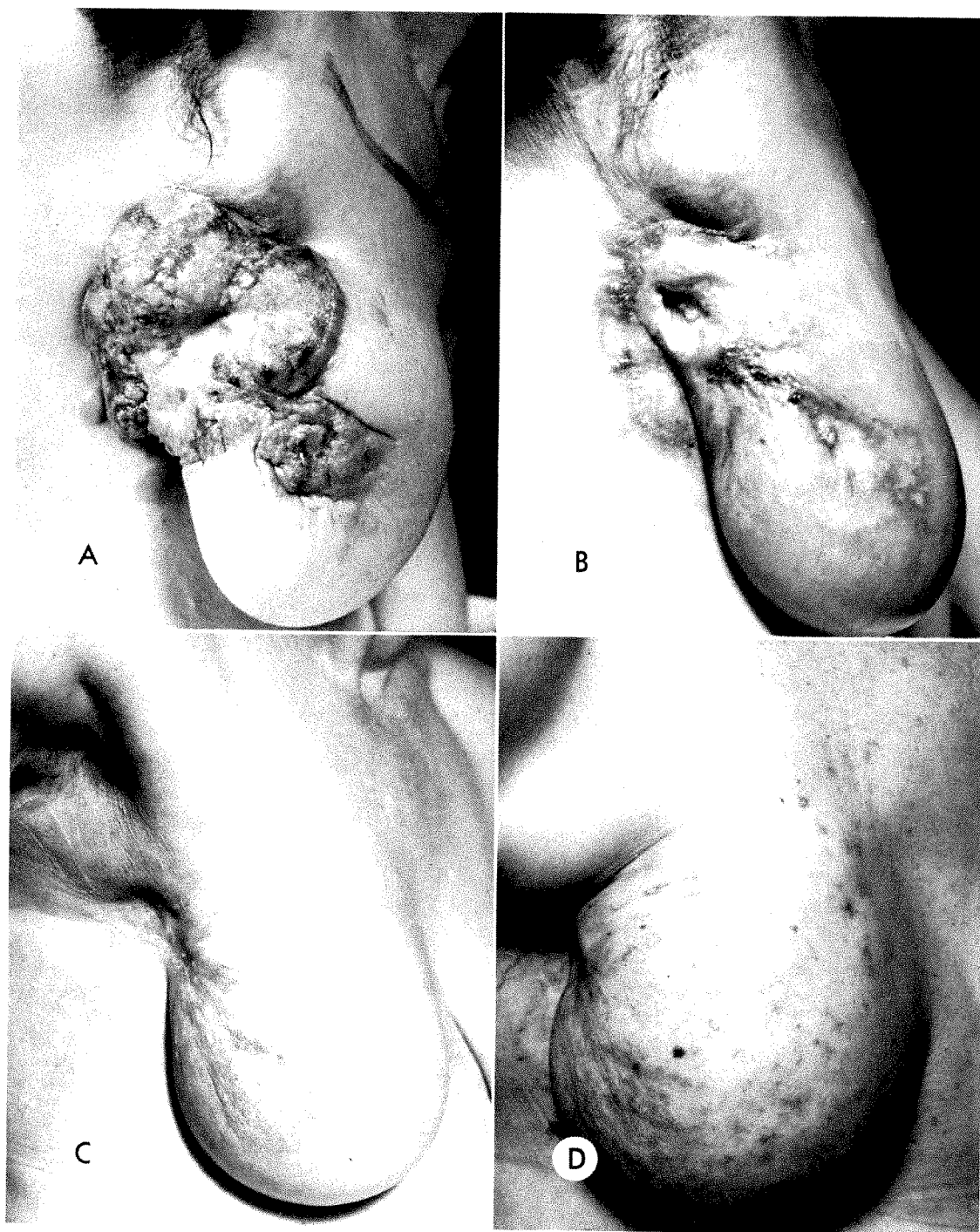


FIG. 3. Case 1, F.H. (A) February 2, 1957. This patient noted a gradually enlarging mass in her right breast for a period of 2 years. When first seen, there was a 10×15 cm. fungating, ulcerating mass involving the entire outer one-half of the breast. She had multiple skin metastases, palpable axillary and supraclavicular lymph nodes, and chest roentgenograms showed multiple pulmonary metastases. A biopsy of the breast was positive for carcinoma. On January 31, 1957, she began a 4 day course of rapid radiotherapy with 1,740 r tumor dose delivered to the breast and 1,840 r tumor dose to the lymph node area. She was also treated by radiation castration at that time, receiving 1,200 r tumor dose through opposing anterior and posterior betatron pelvic portals. (B) April 5, 1957. Two months following completion of radiotherapy,

TABLE I
PATIENT MATERIAL AND AREAS TREATED WITH RAPID RADIOTHERAPY

Patients Treated			Areas Treated				
Stage	Surgical Status	No. of Patients	Breast, Axilla and Supra-clavicular Region	Breast and Supra-clavicular Region	Breast	Axilla and Supra-clavicular Region	Supra-clavicular Region
I	Medically inoperable	1	1	0	0	0	0
	Postoperative, recurrence	5*	2	0	0	2	1
	Postoperative, simple mastectomy	3	3	0	0	0	0
	Stage I Total	9	6	0	0	2	1
II	Postoperative, simple mastectomy	2	1	0	0	1	0
III	Surgically inoperable	10	10†	0	0	0	0
	Postoperative, simple mastectomy	2	1	0	0	1	0
	Stage III Total	12	11	0	0	1	0
IV	Surgically inoperable	23	16‡	3	4	0	0
	Postoperative, simple mastectomy	1	0	0	0	1	0
	Stage IV Total	24	16	3	4	1	0
All Patients		47	34	3	4	5	1

* Postoperative recurrences consisted of metastases only to lymph nodes in 2 cases, mastectomy scar recurrent tumor in 1 case and 2 cases in which large nodal recurrences and skin metastases with ulceration occurred.

† One Stage III patient was retreated with rapid radiotherapy to the breast.

‡ One case of Stage IV carcinoma of the male breast is included. Both breasts were treated in one Stage IV patient with bilateral carcinoma. The breast was retreated with rapid radiotherapy in one Stage IV patient.

the ulcerated areas had almost healed and the masses had decreased markedly. Since considerable tumor remained, it was elected to re-treat the breast. On April 8, 1957, she began a 2 day course of rapid radiotherapy and received 1,760 r tumor dose to the breast through opposing tangential fields. (C) *January 29, 1958*. Following the second course of radiotherapy, there was evidence of further tumor regression. She was placed on hormonal therapy and remained on this medication 5½ years. Asymptomatic pulmonary fibrosis of the right upper lobe was discovered in December, 1961. (D) *July, 1962*. Palpable masses in the breast and axilla were gradually replaced by massive fibrosis of the right breast. Osteolytic metastases in the lumbar spine and sacroiliac areas were treated with cobalt 60 with good relief of symptoms in July, 1962. The patient expired with metastatic carcinoma on October 15, 1962. At no time was there evidence of re-activation of tumor in the treated area.

mary lesions was obtained except for 1 patient who had temporary or no control of her carcinoma before dying of widespread metastases 7 months after radiotherapy.

Two Stage IV patients are alive with good local control of their carcinomas, 1 with evidence of metastatic carcinoma 17 months after rapid radiotherapy, and the other clinically free of carcinoma 60 months following completion of radiotherapy. Repeated chest roentgenograms on the latter patient demonstrated no change in pulmonary radiodensities, diagnosed originally as metastatic lesions, and it is now felt that the patient had hematogenous spread of granulomatous disease and that she is, in actuality, a Stage III patient. The remaining 22 Stage IV patients have succumbed to metastatic carcinoma after an average survival of 12 months post radiotherapy. In 20 of these patients, good control of the carcinomas in the

treated areas was obtained, while in the remaining 2 partial control of local disease was achieved.

An over-all survival rate of 17 per cent (4.2 per cent with persistent distant tumor and 12.8 per cent with no evidence of carcinoma) was noted in the 47 patients treated.

C. COMPLICATIONS

Table IV shows the incidence of the complications* observed with rapid radiotherapy of the breast. Not listed are the local radiation reactions immediately following radiotherapy, such as transient edema, erythema, moist or dry epidermitis, and later development of subcutaneous fibrosis in the areas treated. These local reactions to radiotherapy occurred in 75

* The term "significant complications" is designated to include "frozen shoulder," "painful shoulder," radiation pneumonitis and pulmonary fibrosis (including asymptomatic cases), lymphedema of the arm and necrosis of bone or breast.

TABLE II
CONTROL OF CARCINOMA IN THE TREATED VOLUME

Patients Followed*			Control of Irradiated Areas†		
Stage	Surgical Status	No. of Patients	Good	Partial	Temporary or None
I	Medically inoperable	1	1	0	0
	Postoperative, recurrence	5	4	0	1
	Postoperative, simple mastectomy	3	2	0	1
	Stage I Total	9	7	0	2
II	Postoperative, simple mastectomy	2	2	0	0
III	Surgically inoperable	7	6	0	1
	Postoperative, simple mastectomy	2	2	0	0
	Stage III Total	9	8	0	1
IV	Surgically inoperable	21	19	2	0
	Postoperative, simple mastectomy	1	1	0	0
	Stage IV Total	22	20	2	0
All Patients		42	37	2	3

* Three Stage III patients and 2 Stage IV patients were lost to follow-up.

† *Good control*—permanent improvement as evidenced by decrease in inflammatory elements, healing of ulcerations, decrease in size of tumor mass and alleviation of pain or other local symptoms. *Partial control*—incomplete regression of masses, healing ulcerations, partial decrease in inflammatory elements or local symptoms. *Temporary or no control*—brief or short-lived control or no change in treated areas.

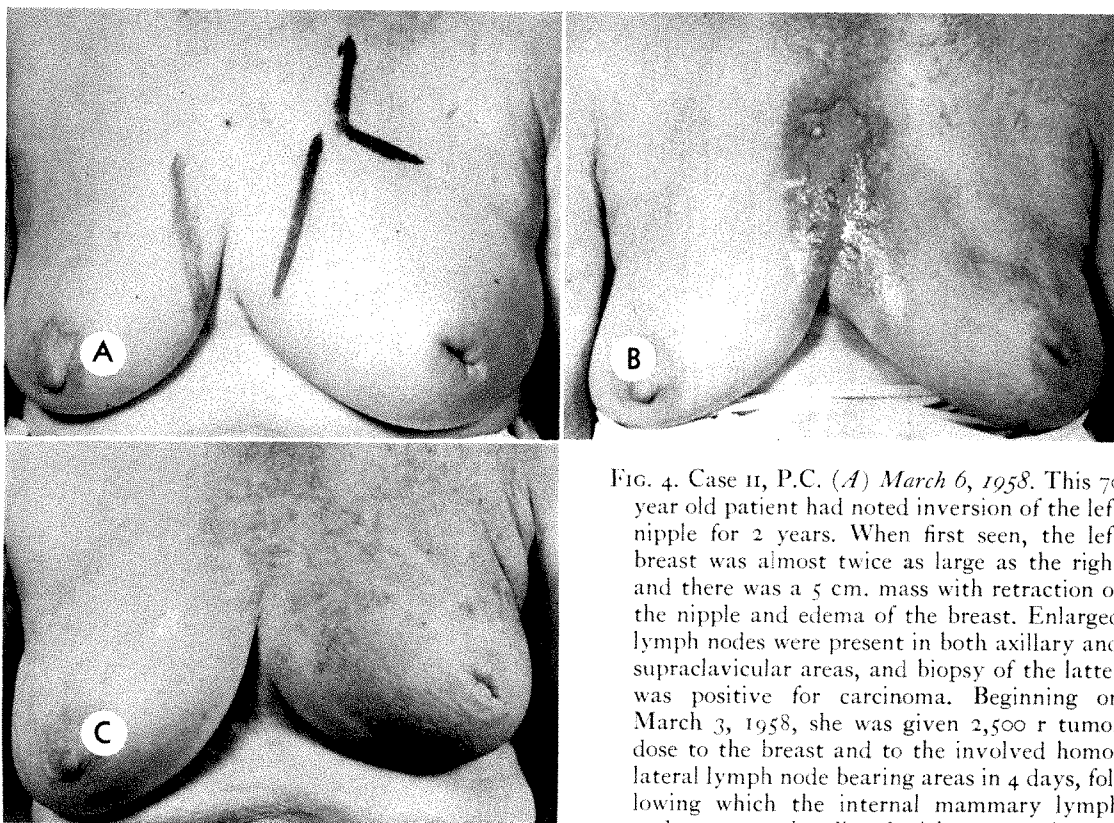


FIG. 4. Case 11, P.C. (A) *March 6, 1958.* This 70 year old patient had noted inversion of the left nipple for 2 years. When first seen, the left breast was almost twice as large as the right and there was a 5 cm. mass with retraction of the nipple and edema of the breast. Enlarged lymph nodes were present in both axillary and supraclavicular areas, and biopsy of the latter was positive for carcinoma. Beginning on March 3, 1958, she was given 2,500 r tumor dose to the breast and to the involved homolateral lymph node bearing areas in 4 days, following which the internal mammary lymph node area was irradiated with 3,750 r air dose

in 21 days using 250 kv. roentgen rays. (B) *April 23, 1958.* There was rapid regression of the primary tumor and metastatic lymph nodes. One month following therapy the breast was almost normal in size, although the nipple remained inverted. There was minimal skin reaction over the breast and lymph node areas, while the sternal port exhibited a moderate moist epidermitis. (C) *December 11, 1958.* Minimal decreased motion of the left arm was present 6 months after completion of radiotherapy and progressed to a frozen shoulder by December 11, 1958. At this time, there was obvious fibrosis of the subcutaneous tissues on the left, and the left breast was smaller than the right. The patient was otherwise well until January, 1960, when she became weak and progressively deteriorated. The patient expired in a nursing home with carcinomatosis on August 8, 1960, with continued control of the tumor in the treated area until the time of death.

per cent of the patients observed. Massive late fibrosis of the breast occurred in all of the long term survivors but has not been a "significant" complication (Fig. 3 through 5, inclusive). Two patients developed extensive keratoses in the treated volume 4 to 5 years after completion of radiotherapy. No evidence of new malignancy in the treated areas has been noted to date.

"Frozen shoulder" occurred in 18 patients and was thought to be a sequela of peri-articular fibrosis (*i.e.*, pectoral and deltoid muscles, etc.) rather than an intra-articular phenomenon. Most of the patients having frozen shoulder had subsequent

atrophy of the musculature of the shoulder girdle and upper extremity on the side irradiated. Beginning in 1961, the shoulder was excluded from the treated volume in an effort to decrease the incidence and severity of frozen shoulders (Fig. 1, A and B; and 2, A and B). Of 8 patients treated in 1961 and 1962, 4 have developed stiff shoulders but this complication has been less severe in degree than the "frozen shoulder" in patients treated prior to 1960. The onset of stiffness of the shoulder was noted from 4 months to 2 years after completion of rapid radiotherapy but most often occurred 8 months or longer following radiotherapy.

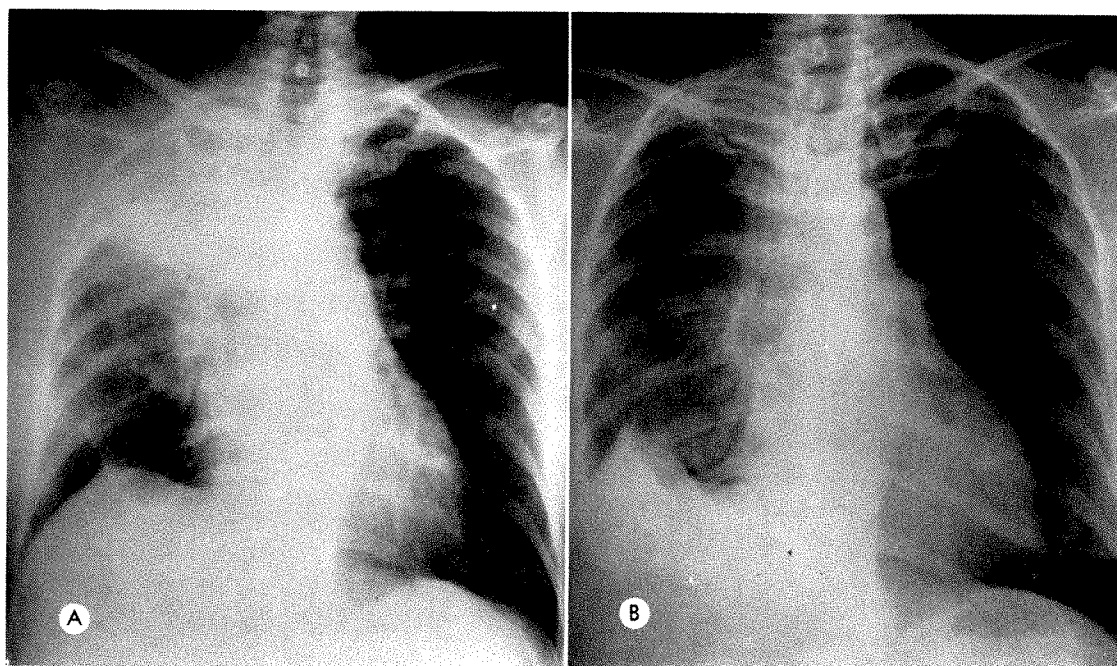


FIG. 5. Case III, N.B. May 25, 1959. (A) Supine and (B) erect roentgenograms of the chest of a 56 year old patient $5\frac{1}{2}$ months following rapid radiotherapy for Stage I carcinoma of the right breast (inoperable because of severe rheumatic heart disease). The patient had an excisional biopsy of a 2 cm. mass which demonstrated adenocarcinoma with tumor remaining in the margins of the biopsy. In December, 1958, the patient was treated with 2,500 r tumor dose to the breast and lymph node areas (2 days to each area). A mild erythema at completion of therapy had progressed to moist epidermitis at 1 month and had cleared 2 months following radiotherapy. On May 25, 1959, the patient reported cough and mild shortness of breath, and chest roentgenograms demonstrated fibrosis and pneumonitis of the right upper lobe with right pleural effusion. By 9 months after radiotherapy, symptoms were alleviated although pulmonary fibrosis was still present on the roentgenograms.

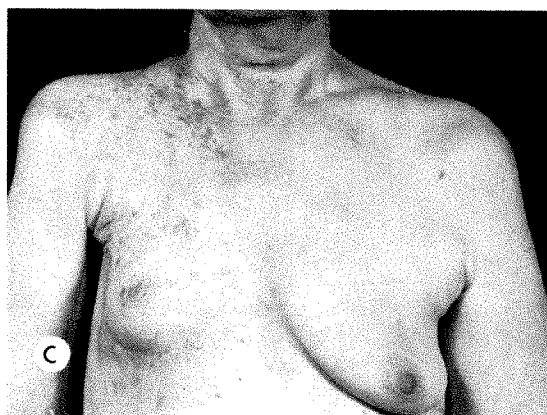


FIG. 5. (C) February 24, 1964. In August, 1959, lymphedema and limitation of the right arm to abduction were noted; these have persisted to date. Atrophy of the right shoulder and arm was noted 20 months after completion of radiotherapy and was associated with pain and tingling of the right hand. These latter symptoms were relieved

Pain in the upper extremity, tingling in the fingers or other local neurologic symptoms were associated with frozen shoulders in 6 patients. Two patients had painful shoulders without significant limitation of motion. One was proved to have a humeral head metastasis; the other had marked lymphedema of the arm, and it was felt the pain was secondary to vasomotor difficulties. No patient developed a severe neuro-

after the patient had been placed on hormonal therapy. Keratoses of the skin in the treated areas were noted 40 months after radiotherapy. On follow-up no evidence of basal cell degeneration in the treated areas has been noted. A recent follow-up examination showed no evidence of carcinoma.

TABLE III

SURVIVAL

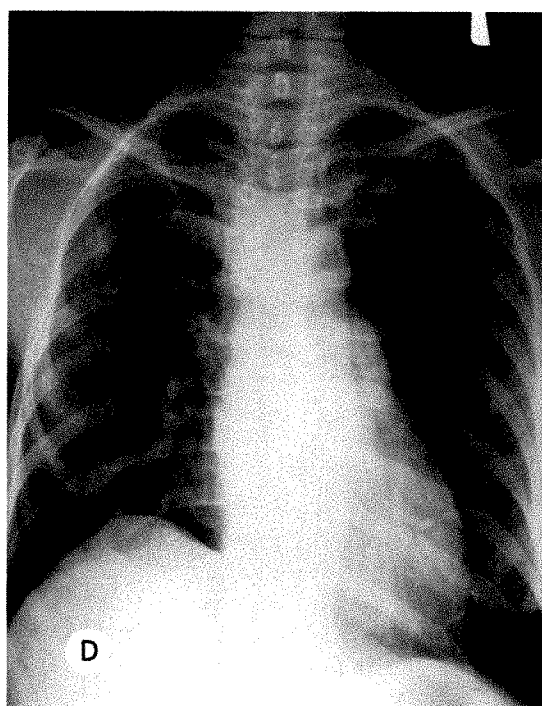
Patients Treated			Survival		Deceased	
Stage	Surgical Status	No. of Patients	With Distant Disease	Without Disease	With Distant Disease	Without Disease
I	Medically inoperable	1	0	1	0	0
	Postoperative, recurrence	5	0	2	3	0
	Postoperative, simple mastectomy	3	0	2	1	0
	Stage I Total	9	0	5	4	0
II	Postoperative, simple mastectomy	2	0	0	2	0
III	Surgically inoperable	10	0	0	10	0
	Postoperative, simple mastectomy	2	1	0	1	0
	Stage III Total	12	1	0	11	0
IV	Surgically inoperable	23	1	1	21	0
	Postoperative, simple mastectomy	1	0	0	1	0
	Stage IV Total	24	1	1	22	0
All Patients		47	2	6	39	0

logic complication, such as cervical or dorsal myelitis.

Roentgenographic findings of acute pneumonic infiltrates with occasional pleural effusions and late findings of pulmonary fibrosis involving irradiated portions of the lung were noted in 12 patients (Fig. 5). The pleuropulmonary complications usually occurred in an asymptomatic patient, and the most severe respiratory symptoms were



FIG. 5. (D) February 24, 1964. An erect chest roentgenogram demonstrated resorption of bone of the right second through sixth ribs and fractures of the posterior portions of the right second, fifth and sixth ribs, with evidence of healing since examination 6 months earlier. No pain was associated with these osseous lesions. Radionecrosis of the ribs was diagnosed in this patient since no areas of osteolysis outside of the treated areas or other evidence of metastatic disease were found.



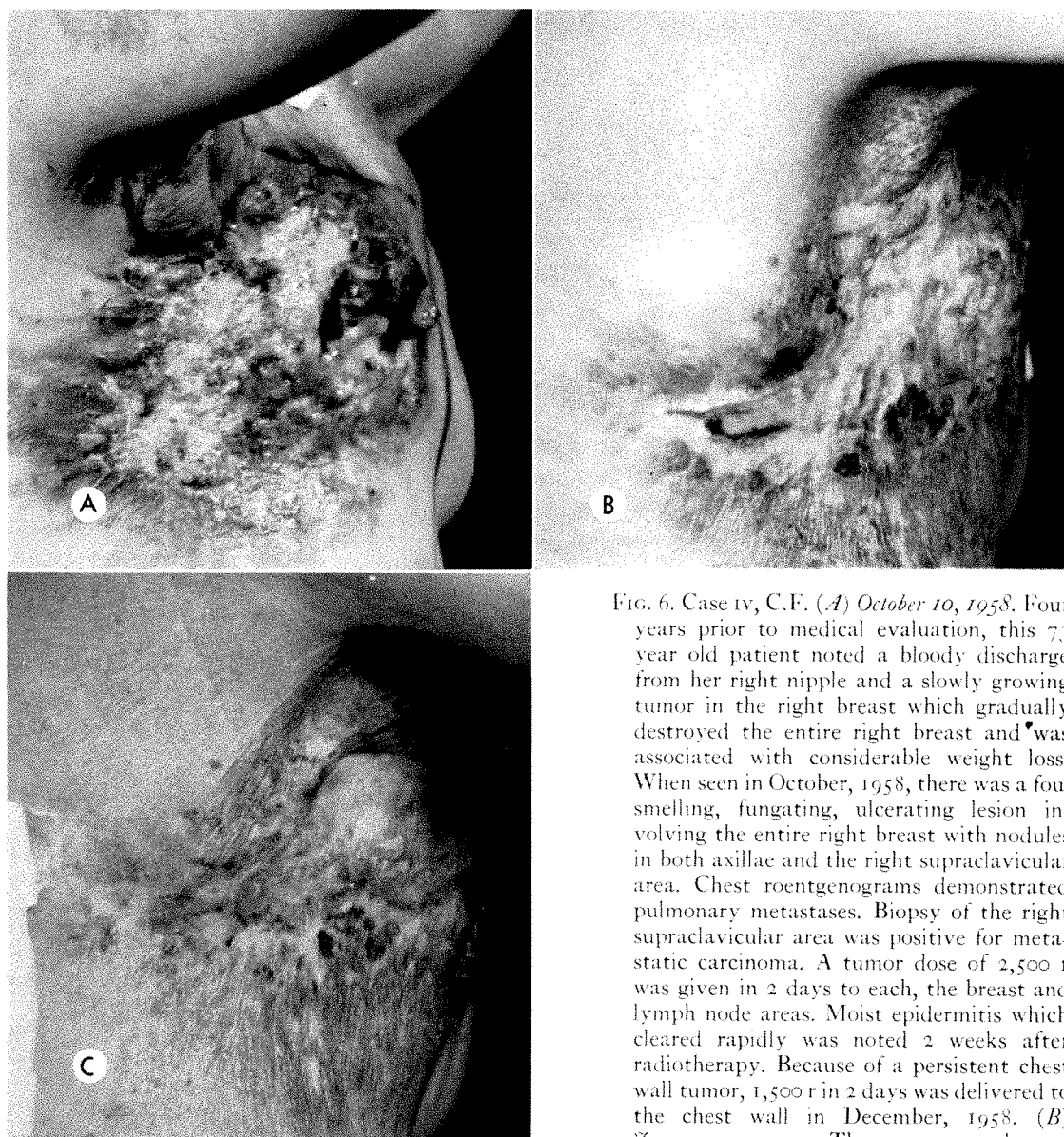


FIG. 6. Case IV, C.F. (A) October 10, 1958. Four years prior to medical evaluation, this 73 year old patient noted a bloody discharge from her right nipple and a slowly growing tumor in the right breast which gradually destroyed the entire right breast and was associated with considerable weight loss. When seen in October, 1958, there was a foul smelling, fungating, ulcerating lesion involving the entire right breast with nodules in both axillae and the right supraclavicular area. Chest roentgenograms demonstrated pulmonary metastases. Biopsy of the right supraclavicular area was positive for metastatic carcinoma. A tumor dose of 2,500 r was given in 2 days to each, the breast and lymph node areas. Moist epidermitis which cleared rapidly was noted 2 weeks after radiotherapy. Because of a persistent chest wall tumor, 1,500 r in 2 days was delivered to the chest wall in December, 1958. (B) January 14, 1959. The masses on the pa-

tient's chest wall decreased in size while progressive enlargement of the pulmonary metastases was noted. (C) April 13, 1959. Six months following initial radiotherapy the ulcerations were healed completely with excellent regression of the breast masses. The patient succumbed to carcinomatosis on July 15, 1959.

those of mild shortness of breath or slight cough.

The third most frequent complication noted was lymphedema of the arm on the treated side, which occurred in 11 patients, none of whom had operative procedures which could have produced venous or lymphatic obstruction to the upper extremity (Fig. 5, A-D). No cases of sarcomatous de-

generation in patients with lymphedema were noted. The lymphedema was thought to be secondary to obstruction of lymphatic or venous flow by massive fibrosis in these patients, but obstruction by tumor cannot be excluded as a possibility.

Five patients developed necrosis of the ribs in the treated volume (Fig. 5D). The general appearance of the areas of osteo-

necrosis was that of bone resorption without sclerosis or sequestration, accompanied by pathologic fractures. Asymptomatic radionecrosis of the ribs occurred in 3 Stage I patients, and in 1 Stage III patient. All of these patients had obtained permanent control of the treated areas, although 2 patients eventually succumbed to metastatic carcinoma, 5 months and 17 months following radiotherapy. Two Stage I patients with asymptomatic radionecrosis of bone have survived 60 and 63 months after radiotherapy with no evidence of carcinoma present. One Stage I patient treated post-operatively, following a simple mastectomy, developed marked necrosis of the anterior chest wall due to locally recurrent tumor at the same time that radionecrosis was observed involving the posterior portions of the ribs on the treated side. This patient died of carcinomatosis 39 months after radiotherapy.

A single Stage III patient had necrosis of the intertriginous undersurface of the treated breast after initial good local control of the carcinoma. No evidence of per-

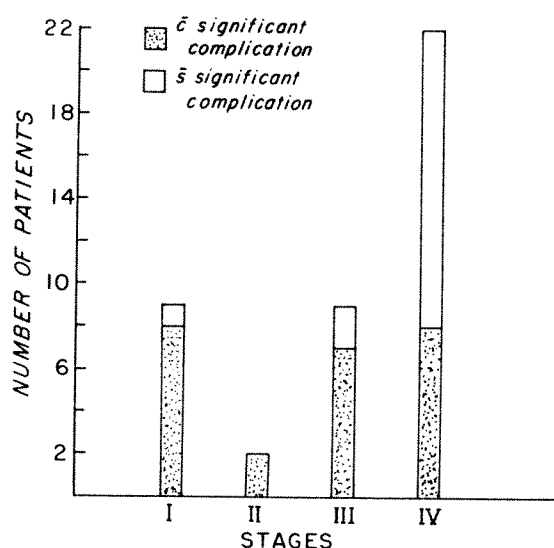


FIG. 7. Clinical stages of carcinoma of the breast treated with rapid radiotherapy compared with the complication rate. Note the high percentage of "significant" complications in the earlier cases and the relatively lower complication rate in the Stage IV cases.

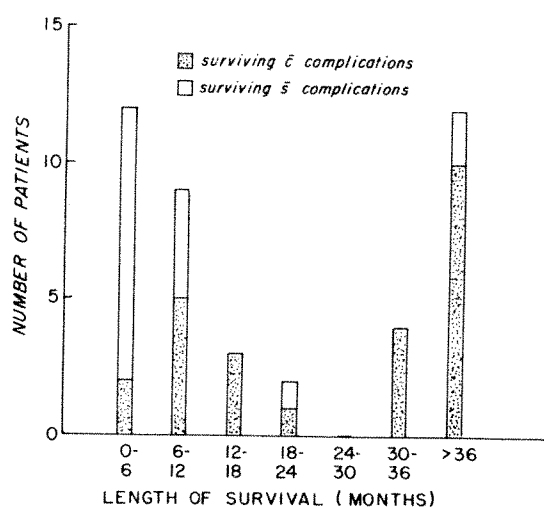


FIG. 8. Length of survival of patients treated with rapid radiotherapy correlated with the complication rate. Note the few complications occurring in patients surviving less than 1 year and the high number of "significant" complications in patients surviving over 1 year.

sistent tumor was noted in this patient, but, unfortunately, she was lost to follow-up after 1 year, and died with widespread carcinoma 2½ years after radiotherapy.

Mild dysphagia was observed following rapid therapy in 2 patients. Symptoms cleared in both patients and they had no difficulty in swallowing 3 weeks after completion of therapy. No severe esophagitis or stricture formation was noted in patients undergoing rapid therapy.

In general, complications seemed to correlate well with survival and stage of disease. The highest complication rate occurred in patients with early stage carcinomas (Fig. 7) and in those surviving the longest (Fig. 8). The lowest complication rate occurred in Stage IV patients and in those surviving less than 1 year.

DISCUSSION

Rapid radiotherapy is a method of quickly controlling advanced cases of carcinomas of the breast. Patients with a poor prognosis can be given palliation without the necessity of a costly prolonged hospitalization or numerous outpatient trips to the radiotherapy department.

The theoretic basis of rapid radiotherapy has been alluded to by several authors⁶⁻⁹ in studies of the time-dose relationships in radiotherapy of carcinoma of the breast. Either the median lethal dose (LD_{50}) or the 90 per cent tumor curative dose can be calculated by using the formula⁶: $D = E \cdot T^n$ where D is the total absorbed dose (tumor dose); T is the number of fractions; E is the single dose required to produce a specific effect, such as median lethal dose (LD_{50}), and n is a "recovery exponent." Since the "recovery exponents" of breast carcinoma and skin are close to equal ($n = 0.33-0.35$),^{6,8,9} prolonged fractionation in breast carcinoma may be considered to be theoretically unnecessary. Squamous cell carcinoma, however, has a slower recovery rate ($n = 0.25$) than skin, and fractionation in these cases seems more logical.

Cohen⁶ treated 60 cases of breast carcinoma with varying doses and fractionations and concluded that the median curative single dose for breast carcinoma was 1,270 r (orthovoltage) and found that an iso-effect curve for his patients correlated well with curves obtained by other authors. Using Cohen's formula, the calculated 50 per cent curative dose for 2 treatments is 1,580 r (orthovoltage). This is equivalent to 1,900 r in 2 doses administered with a 22.5 mev. betatron roentgen-ray beam because of the lesser relative biologic effectiveness of the supervoltage modality. The single 90 per cent curative dose was estimated by Cohen⁶ to be 1,500 r (orthovoltage). By similar calculations, a total tumor dose of 2,250 r in 2 fractions using supervoltage equipment should sterilize the tumor in 90 per cent of the cases.

Friedman and Pearlman⁹ treated 29 patients with metastatic skin nodules of breast carcinoma with varying dosages and fractions. The minimum observed "tumor lethal doses" varied from 1,800 r to 3,000 r (orthovoltage) with an average of 2,200 r. They constructed a free hand iso-effect curve of tumor shrinkage and on this basis concluded that 2,000 r was the single exposure "minimum tumor lethal dose" and

the recovery exponent was $n = 0.25$. De-Moor *et al.*⁷ analyzed the data of Friedman and Pearlman⁹ and noted that the findings could equally fit a curve originating at $E = 1,600$ r with $n = 0.34$; since the data represented the LD_{90} , it was felt that they are in excellent agreement with the data of Cohen.⁶

In the current series, doses of 2,500 r in 2 days were adequate to control the primary tumor, metastatic nodules, and involved lymph nodes in 88 per cent of the patients. These results correlate well with the theoretic data presented above. However, the observed reactions in normal tissue in a large portion of these patients suggest that with this method no differential effect exists as regards tumor tissue and normal tissue.

The high rate of control of tumor in the irradiated volume (88 per cent) with few instances of tumor reactivation (12 per cent) contrasts favorably with the results of other investigators using rapid treatment.^{3,10,11,12} Stoll¹² described healing of ulcerations in all cases in which this finding was noted, but reported a tumor reactivation rate of 48 per cent, with sustained control of the tumor in only 52 per cent of the cases. Atkins¹ noted complete control in 11 of 18 cases (61 per cent), partial control in 4 cases (22 per cent), and no control in 3 cases (17 per cent). Because of the sustained good control of the lesion in a high percentage of our patients, we have adopted rapid radiotherapy as the treatment of choice for Stage IV patients.

After initial success with local control of carcinoma in palliative cases,⁵ patients with less advanced stages of carcinoma were treated. Consequently, the complication rate rose. As previously indicated, the complication rate is correlated with a longer survival in these earlier stages.

In Table IV, it may seem that the complication rate was higher in patients who had mastectomies, as opposed to patients in whom no surgery was done. It is felt that this comparison is not a valid one because patients undergoing mastectomies had earlier stage carcinomas than the patients not

TABLE IV
COMPLICATIONS

Patients Followed*			No. of Patients with "Significant" Complications	Total Number of Complications				
Stage	Surgical Status	No. of Patients		"Frozen" Shoulder	Radiation Pneumonia and Pulmonary Fibrosis	Lymph-edema of Arm	Necrosis of Bone or Breast	Other†
I	Medically inoperable	1	1	1 (1)‡	1	0	1	1
	Postoperative, recurrence	5	4	2 (2)	1	1	2	1
	Postoperative, simple mastectomy	3	3	2 (1)	3	2	1	0
	Stage I Total	9	8	5 (4)	5	3	4	2
II	Postoperative, simple mastectomy	2	2	2 (2)	1	1	0	0
III	Surgically inoperable	7	5	5 (0)	2	4	1	1
	Postoperative, simple mastectomy	2	2	2 (1)	1	1	1	0
	Stage III Total	9	7	7 (1)	2	5	2	1
IV	Surgically inoperable	21	8	4 (1)	3	2	0	1
	Postoperative, simple mastectomy	1	0	0 (0)	0	0	0	0
	Stage IV Total	22	8	4 (1)	3	2	0	1
All Patients		42	25	18 (8)	12	11	6	4

* Three Stage III patients and 2 Stage IV patients were lost to follow-up.

† Other includes mild esophagitis and keratoses developing in the treated volume.

‡ Numbers in parenthesis represent patients who developed shoulder pain, paresthesia, etc.

operated upon. The increased complication rate of the operative cases is felt to be due to the longer survival rate in these earlier stage carcinoma patients.

The complications of rapid radiotherapy are related to the marked development of fibrosis in the treated areas, a feature not as frequently observed with conventional (prolonged fractionation) radiotherapeutic techniques. Most of the "significant" complications observed in the present study are

felt to be related to irradiation through the anterior (lymph node) portal. Use of the tangential (breast) portals may contribute slightly to the fibrosis around the shoulder joint, but otherwise causes no difficulty (except for the rare case of breast necrosis). These observations appear to be substantiated by Stoll¹² who treated 44 patients with inoperable carcinoma of the breast, using only long tangential ports and rapid massive doses of supervoltage roentgen rays.

Complications consisted of frozen, painful shoulder in 3 cases and 1 case of chest wall necrosis. No pulmonary, esophageal, laryngo-tracheal or spinal cord complications were noted. In a later series, Stoll¹⁸ changed his technique by shortening the tangential fields and adding a large anteroposterior supraclavicular port and noted a great deal of fibrosis in the pectoral muscles anterior to the shoulder joint.

Although the complication rate in the current series appears high, many of the complications listed are minor, *i.e.*, asymptomatic and mildly symptomatic radiation pneumonia and pulmonary fibrosis, mild stiffness of the shoulder, mild lymphedema or asymptomatic radionecrosis of ribs, as compared with the complications reported in other series.^{1,2,10} Most of the complications occurred in patients with early stage carcinoma (Fig. 7); in general, the longer the survival period, the greater the percentage of patients with complications (Fig. 8).

Horrigan *et al.*¹⁰ and Atkins,^{1,2} using a method of radiotherapy for carcinoma of the breast similar to the one employed in the current series, reported more severe complications. Of 18 patients treated, Atkins reported 4 cases of radiation myelitis, 2 cases of vocal cord palsy, 9 cases of esophagitis (1 of which had late esophageal stricture formation), in addition to the pulmonary fibrosis and fibrosis around the shoulder observed in the present study.

The technique of rapid radiotherapy used by Atkins¹ is quite similar to the one used in the current investigation. A notable difference is the use by Atkins of a 12×20 cm. portal for irradiation of the lymph node bearing area. The medial border of this portal is placed at the midline but projects beyond the midline by the time it reaches the spine.² It is felt that the high incidence of severe complications reported by Atkins may be related to inclusion of the esophagus, larynx, and spinal cord within the treated volume.

The results obtained in this study have led us now to use rapid radiotherapy as the

treatment of choice in patients with metastases at the time they are first seen. The remaining patients with carcinoma of the breast are being treated with more conservative methods of fractionated radiotherapy.

SUMMARY

1. Between January 1, 1957, and January 1, 1963, 47 patients with inoperable carcinoma of the breast were treated with a method of rapid massive-dose radiotherapy. Utilizing the 22 mev. betatron roentgen-ray beam, 2,500 r tumor dose was delivered to the breast and to the lymph node bearing areas in a 2 day period for each region (total of 4 days).

2. Local control of the areas treated was good in 88 per cent of the patients.

3. Massive fibrosis in the irradiated areas led to complications of "frozen" shoulder, lymphedema, and radiation pneumonia and pulmonary fibrosis, with only the first two causing symptoms. Necrosis of the ribs or breast was infrequent. No life endangering or incapacitating symptoms occurred. Complications were noted with the highest frequency in patients with early stage carcinomas and in patients surviving more than 1 year.

4. The time-dose relationship for carcinoma of the breast is discussed. Theoretically, protraction of dosage in carcinoma of the breast is unnecessary to achieve permanent local control of the tumor. However, the observed changes in the normal tissues suggest that there is no significant differential benefit from this rapid treatment.

5. Rapid radiotherapy as described is the method of choice for local control of Stage IV breast cancer patients, and it is recommended that this mode of treatment be restricted to patients with short term prognoses.

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THE EFFECT OF RADIATION THERAPY ON THE SURVIVAL TIME OF WOMEN WITH RECURRENT MAMMARY CARCINOMA*

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IN THE management of recurrent carcinoma of the breast following mastectomy, hormonal and radiation therapy are the two major modalities of treatment. It is well known that radiation therapy is effective in the control of local recurrence and in offering palliation to symptomatic areas of metastasis. There are few available data, however, to determine whether radiation therapy given for recurrent disease has a beneficial effect, no effect, or a deleterious effect on the patient's life span. The purpose of this paper is to explore this problem by a retrospective study reviewing and analyzing the data of the survival times of 656 patients treated for recurrent mammary carcinoma.

MATERIAL

The material consisted of the records of over 700 deceased patients with recurrent mammary carcinoma seen in the Hormonal Therapy Clinic of the Memorial Hospital over the last 18 years. After exclusion for various reasons, such as questionable diagnosis, inadequate follow-up, and non-simultaneous bilateral carcinomas of the breast, 656 cases were found suitable for analysis. All patients had recurrent mammary carcinoma following definitive surgery of the primary tumor which consisted of radical mastectomy in 94 per cent of the cases; the remaining 6 per cent had radical mastectomy with chest wall resection, modified radical mastectomy or simple mastectomy. Of these 656 patients, 423 re-

ceived therapeutic irradiation to one or more sites of recurrent disease, 93 per cent of whom had their first course of irradiation within the first year of recurrence, and 233 did not receive radiation treatment at any time following the initial appearance of recurrence.

These two groups of cases, patients who were given radiation therapy for recurrent mammary carcinoma and those who were not, formed the basis of this analysis. Prophylactic postoperative radiation therapy had been given to 223 patients of the irradiated group (53 per cent) and to 161 patients of the nonirradiated group (69 per cent). All patients in both groups received some form of hormonal therapy, additive or ablative, during the course of the recurrent disease.

DEFINITIONS

The following definitions are used in this paper:

Recurrence. The term "recurrence" is used to indicate reappearance of cancer after mastectomy as evidenced either by local recurrence and/or distant metastases.

Cancer Free Period. This is the time from mastectomy to the clinical detection of recurrence.

Type of Recurrence. Patients who developed recurrence after mastectomy were classified into 3 categories depending on the type of the initial recurrent lesions: (1) *local dominant*, if skin nodules, regional or distant, or metastasis to lymph nodes or

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TABLE I
DISTRIBUTION OF CASES BY CANCER FREE PERIOD

	Total No. of Patients	0-12 mo.	13-24 mo.	25-36 mo.	37-48 mo.	49-60 mo.	61 mo.
Radiation Therapy	423	32%	27%	13%	10%	7%	11%
No Radiation Therapy	233	29%	27%	13%	8%	9%	14%

opposite breast were the presenting signs of recurrence; (2) *osseous dominant*, if skeletal metastases were the presenting signs of recurrence; or (3) *visceral dominant*, which consisted of metastases to liver, or other intra-abdominal viscera, brain, pleura, lung or mediastinum.

When at the time of first recurrence there were more than one dominant lesion present, the classification gave precedence to visceral over osseous, and osseous over local.

Survival time was determined from the time of recognition of the recurrence to death.

EVALUATION AND RESULTS

A. PRELIMINARY CONSIDERATIONS

From previous reports in the literature,¹⁻⁵ the survival of patients with recurrent mammary carcinoma appears to be influenced by several factors. Among them are the length of the cancer free period, the menstrual status of the patients, the type of recurrence and the response to hormonal therapy. The length of the cancer free period reflects to some degree the natural history of the cancer in that the shorter the

cancer free period, the shorter the life span of the patients.^{1,5} The menstrual status at the time of recurrence also influences the patients' survival. According to Escher and Kaufman,¹ patients 0-5 years postmenopausal appeared to have a poorer prognosis than those who were menstruating or were more than 5 years postmenopausal. There is agreement that the type of recurrence plays a major role in prognosis.^{1,4,5} Patients with local dominant recurrence have the best prognosis. Those with osseous dominant recurrence have less chance for prolonged survival, and those with visceral dominant lesions have a markedly worse outlook. Finally, the response to hormonal therapy, additive or ablative, is considered an outstanding factor influencing the survival of patients with recurrent mammary carcinoma. Reports in the literature¹⁻⁵ indicate that the average survival period of patients with responsive disease was about twice as long as that of patients who did not derive any benefit from hormonal therapy.

Before evaluating the effects of radiation therapy on patients' survival time, the above factors were analyzed to deter-

TABLE II
DISTRIBUTION OF CASES BY MENSTRUAL STATUS

Menstrual Status at Recurrence	Radiation Therapy		No Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Menstruating	153	36	69	30
0-5 yr. post menopausal	112	26	49	21
6-10 yr. post menopausal	58	14	32	14
>11 yr. post menopausal	100	24	83	35
Total	423	100	233	100

TABLE III
DISTRIBUTION OF CASES BY DOMINANT
SITE OF RECURRENCE

Dominant Lesion at Recurrence	Radiation Therapy		No Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Local	209	49	37	16
Osseous	135	32	72	31
Visceral	79	19	124	53
Total	423	100	233	100

mine any influence on the two groups of patients, those with and those without irradiation.

Cancer Free Period. The two groups of patients were comparable as far as the cancer free period was concerned. The distribution was similar in both series (Table I).

Menstrual Status. The two groups were comparable as shown in Table II.

Type of Recurrence. The distribution of cases according to the dominant site of recurrence was uneven (Table III). There was a larger proportion of local dominant cases in the irradiated series, and a larger

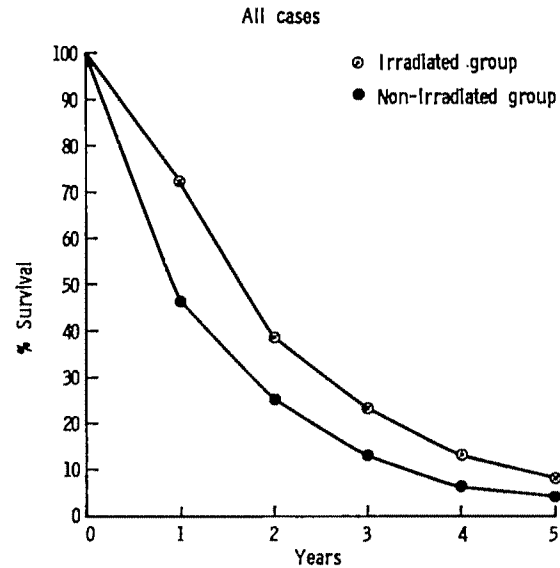


FIG. 1. Survival in years after recurrence.
All cases.

proportion of visceral dominant cases in the nonirradiated series. It was, therefore, necessary to subdivide the two series, and to compare them according to the dominant site of recurrence.

Hormonal Response. The distribution of cases according to hormonal response was about equal in both groups: 75 of the 423 patients, or 18 per cent, in the irradiated

TABLE IV
SURVIVAL IN YEARS AFTER RECURRENCE—ALL CASES

		No. of Patients	1 Year		2 Years		3 Years		4 Years		5 Years	
			No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Radiation Therapy	Total	423	305	72	160	38	95	23	52	12	33	8
	Hormonal Failure	349	232	67	111	32	62	18	29	8	19	5
	Hormonal Response	74	73	99	49	66	33	45	23	31	14	19
No Radiation Therapy	Total	233	106	46	57	25	31	13	14	6	10	4
	Hormonal Failure	199	73	37	30	15	13	7	5	3	3	2
	Hormonal Response	34	33	97	27	80	18	53	9	27	7	21

TABLE V
SURVIVAL IN YEARS AFTER RECURRENCE—LOCAL DOMINANT CASES

	Evaluation of Hormone Therapy	No. of Cases	1 Year		2 Years		3 Years		4 Years		5 Years	
			No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Radiation Therapy	Total	209	160	77	96	46	63	30	37	18	25	12
	Hormonal Failure	174	125	72	70	40	43	25	22	13	17	10
	Hormonal Response	35	35	100	26	74	20	57	15	43	8	23
No Radiation Therapy	Total	37	16	43	10	27	5	14	1	3	1	3
	Hormonal Failure	31	10	32	5	16	2	6	1	3	1	3
	Hormonal Response	6	6	100	5	83	3	50	0	0	0	0

series, and 34 of 233 patients, or 15 per cent, in the nonirradiated series had at least one response to endocrine therapy.

B. EVALUATION OF THE EFFECTS OF RADIATION THERAPY ON PATIENTS' SURVIVAL

The over-all yearly survival rate of the two groups of patients is presented in

Table IV and Figure 1. The percentage of survival of patients on a yearly basis was consistently higher in the irradiated group than in the nonirradiated group. Further analysis according to hormonal response revealed that the real difference in survival time as influenced by radiation therapy was in the hormonal failure patients: 67 per

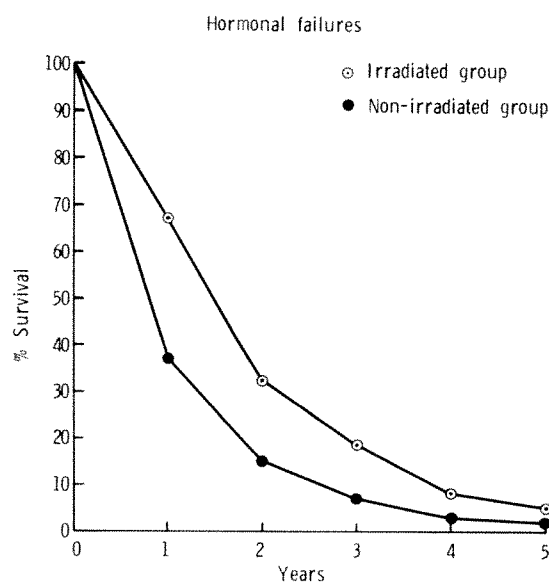


FIG. 2. Survival in years after recurrence, Hormonal failures.

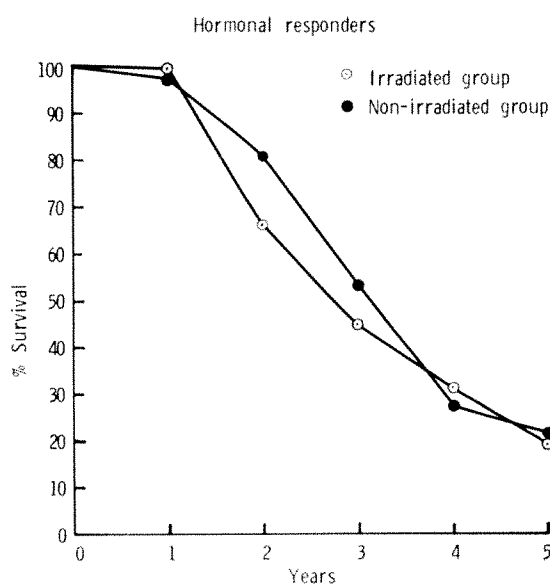


FIG. 3. Survival in years after recurrence, Hormonal responders.

TABLE VI

SURVIVAL IN YEARS AFTER RECURRENCE—OSSEOUS DOMINANT CASES

	Evaluation of Hormone Therapy	No. of Cases	1 Year		2 Years		3 Years		4 Years		5 Years	
			No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Radiation Therapy	Total	135	99	73	45	33	23	17	9	7	4	3
	Hormonal Failure	113	78	69	33	29	16	14	5	5	1	1
	Hormonal Response	22	21	95	12	55	7	32	4	18	3	14
No Radiation Therapy	Total	72	42	58	23	32	12	17	6	8	4	6
	Hormonal Failure	62	32	52	15	24	6	10	2	3	1	2
	Hormonal Response	10	10	100	8	80	6	60	4	40	3	30

cent survived at 1 year and 32 per cent at 2 years in the irradiated group, as against 37 per cent at 1 year and 15 per cent at 2 years in the nonirradiated group. A graphic comparison of the yearly survival rate is presented in Figure 2. In the hormonally responsive patients, the yearly survival

rate was uniformly good in both groups, indicating that the improved survival of these patients was entirely due to hormonal therapy, with no influence from radiation therapy (Fig. 3).

The data were further analyzed according to the type of initial recurrence.

TABLE VII

SURVIVAL IN YEARS AFTER RECURRENCE—VISCERAL DOMINANT CASES

	Evaluation of Hormone Therapy	No. of Cases	1 Year		2 Years		3 Years		4 Years		5 Years	
			No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Radiation Therapy	Total	79	46	58	19	24	9	11	6	8	4	5
	Hormonal Failure	62	29	47	8	13	3	5	2	3	1	2
	Hormonal Response	17	17	100	11	65	6	35	4	24	3	18
No Radiation Therapy	Total	124	48	39	24	19	14	11	7	6	5	4
	Hormonal Failure	106	31	29	10	9	5	5	2	2	1	1
	Hormonal Response	18	17	94	14	78	9	50	5	28	4	22

TABLE VIII
MEAN SURVIVAL IN MONTHS AFTER RECURRENCE

Dominant Lesion at Recurrence	Radiation Therapy			No Radiation Therapy		
	Total	Hormonal Failures	Hormonal Responders	Total	Hormonal Failures	Hormonal Responders
Local	39	28	44	17	13	36
Osseous	24	22	36	21	17	47
Visceral	21	17	35	13	11	42
Total Series	27	24	40	17	13	41

The yearly survival rate of patients with local dominant lesions is presented in Table v. There were 209 patients in the irradiated group and 37 patients in the nonirradiated group. Although the number of patients in the nonirradiated group was small, a trend appeared to be present in that the hormonally unresponsive patients who received irradiation during the course of recurrence lived longer than those who had not. At 1 year after the onset of recurrence, 72 per cent of the hormonal failure patients who received radiation survived *versus* 32 per cent in the nonirradiated group. Further analysis of the 37 cases in which no radiation was given showed that the majority of these patients were suitable for radiation therapy and it was not apparent why it was not given. There was no evidence that these patients' recurrences were more extensive than those of the patients who received radiation treatment.

The survival time of patients with osseous dominant recurrences is presented in Table vi. Again, the survival in the irradiated group was higher than in the nonirradiated group. The 1 year survival of the hormonally unresponsive patients was 78 of 113 patients, or 69 per cent, in the irradiated group, and 32 of 62 patients, or 52 per cent, in the nonirradiated group.

The survival of patients with visceral dominant recurrences is presented in Table vii. Again, a difference in survival was noted: 47 per cent of the patients who had received radiation therapy survived for 1 year after recurrence; only 29 per cent of

patients without radiation therapy lived 1 year.

The mean survival time in months of all patients is summarized in Table viii.

DISCUSSION AND CONCLUSIONS

Although there have been many articles in the literature reporting the survival time of women with mammary carcinoma, most of them deal with the course of the disease from its onset. This report is one of the few which assesses the effect of therapeutic irradiation on the survival of patients after the onset of recurrence. We have found that a beneficial response to hormones has a markedly favorable influence on survival, such that the role of radiation was negligible. In hormonally unresponsive patients, however, radiation therapy appears to affect favorably their life span.

In this study there was good match in the two series in the cancer free period and menstrual status of the patients. Unfortunately, there was an unequal distribution in another of the major prognostic factors on survival, the dominant lesions at first recurrence. However, the data showed marked differences in favor of the irradiated group over the nonirradiated group in survival time for each of the dominant lesion groups. It is tempting to speculate that the improved survival is solely due to irradiation, but it would be unwise to believe that we have controlled all other possible influences on survival. Flaws may always be present in a retrospective study. No firm conclu-

sions can be made from this study. The data appear to indicate some beneficial effect of irradiation on the survival of hormonally unresponsive patients, but no effect on the survival of the hormonally responsive patients. The data are suggestive enough to warrant a prospective study to determine whether or not therapeutic irradiation during the recurrent phase of mammary carcinoma has life prolongation potential.

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PELVIC LYMPHADENECTOMY AS AN ADJUNCT TO RADIATION THERAPY IN TREATMENT FOR CANCER OF THE CERVIX*

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A CLINICAL trial to determine the exact place of lymphadenectomy as an adjunct to radiation therapy in the management of cancer of the cervix was set up in 1957 at The University of Texas M. D. Anderson Hospital as a cooperative effort of the sections of Gynecology and Radiotherapy and the Department of Epidemiology. Enough time has elapsed to present results for the lymphadenectomy and control groups as well as an analysis of the causes of death during the interim. Previous and concurrent experiences with combined and single modality therapy at our institution will be discussed for over-all evaluation of the advantages and hazards involved, together with the implications for areas to be further explored in the future.

The successful management of all but the earliest stages of invasive carcinoma of the uterine cervix concerns therapy to the regional lymph nodes. There is a well-documented literature evaluating sterilization of the lymph nodes by irradiation^{5,6} and the efficacy of surgical extirpation of the regional lymph nodes.² We will attempt to determine whether the prognosis for the patient is improved by the combination of these two methods.

Preceding this study, 100 consecutive patients with Stage III squamous cell carcinoma of the cervix had been subjected to lymphadenectomy following irradiation with 6,000 rads using the 22 mev. betatron to the whole pelvis (including the node-bearing tissues of the obturator, external iliac, hypogastric and lower common iliac lymph nodes at the brim of the pelvis) in an

effort to evaluate the effect of this treatment on sterilization of the lymph nodes. The number of patients showing positive lymph nodes after irradiation indicated that irradiation did not cure all of them. Nor did the lymphadenectomies in this group of patients with advanced disease cure any of those with involved lymph nodes.⁶

Before eliminating lymphadenectomy as an adjunctive procedure, however, it was realized that the selection of patients with the most advanced stage of the disease limited the value of the findings, and that only a study of the total experience randomized by stage of disease with and without adjunctive lymphadenectomy could justify its exclusion or continued use. This would evaluate the procedure in the absence as well as in the presence of positive lymph nodes, since there is a chance for metastasis to be missed unless the specimen is serially sectioned. Specimens 1 through 10 and 50 through 60 in the 100 consecutive lymphadenectomies were serially sectioned, revealing 1 positive case not previously found. This finding would have greater meaning if the specimens studied by serial section had been selected at random.

PLAN OF STUDY

The protocol for the clinical trial called for entry of 60 patients in each of the stages of the disease. These stages were defined as: IA, IB, IIA, IIB, IIIA, and IIIB.

IA—Lesions less than 1 cm. in diameter

IB—Lesions greater than 1 cm. in diameter

IIA—Disease limited to upper two-thirds of vagina,

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TABLE I
CANCER OF THE CERVIX
RANDOM SERIES BY STAGE

Stage	Lymph-adenectomy Group	Control Group	Total	Excluded from Study*
I	30	39	69	10
IIA	39	39	78	7
IIB	25	28	53	7
IIIA	23	28	51	7
IIIB	25	35	60	13
	142	169	311	44

* Physically unsuited.

spread extending not further than the upper third of the vagina and the medial half of the parametrium

II B—Greater extension than IIA

III—Each pelvic wall and the lower third of the vagina are reference points for subdividing Stage III. In substage A, the cancer has reached only one of these points; in substage B, two or more are involved.

All new patients who had not received prior therapy were eligible, except those physically unsuited for the operation, or those with carcinoma of the cervical stump, adenocarcinoma of the cervix or carcinoma complicated by pregnancy. Final determination of stage of disease was made after each patient's course of therapy had been completed. At this point, the Department of Epidemiology determined whether the patient was assigned to the lymphadenectomy group or the control group, according to a previously arranged plan of randomization. It was decided in advance to continue the number of random entries beyond 60 in all stages, in anticipation of probable loss of a small number from unforeseeable complications between the completion of therapy and the planned operation. The first patient was entered in February, 1957, and the last in February, 1960. The total number entered (142 patients in the lymphadenectomy group and 169 in the control group) is shown in Table I by stage of disease. There were 44 exclusions due to complications, of which 13 were in Stage IIIB.

RADIATION THERAPY

The therapy policy (Table II) was established in 1954 at The University of Texas M. D. Anderson Hospital and Tumor Institute and has been consistently followed throughout this study.^{1,7} Intracavitary radium and external roentgen therapy was used according to the stage of the cancer. In Stages IA, IB and IIA, the largest portion of the total dose was administered by intracavitary radium; the remainder was delivered by external irradiation. In all other stages, the largest portion of the total dose was supplied by external irradiation.

The flexibility of radium therapy, permitting close control of location and volume of tissue to be irradiated, makes it the basic approach in controlling cervical cancer. Its rapid fall-off of dose to distant tissues is ideally suited for management of the disease in its primary site. Parametrial external irradiation is not added to radium therapy in Stage IA because the incidence of regional lymph node metastases is low in these patients.

External radiation therapy (supervoltage) in our treatment plan produces a uniform dose distribution throughout the pelvis. The total dose is increased in relation to the degree of the peripheral spread of the disease. External irradiation is the principal mode of therapy in advanced stages of cervical cancer, with a corresponding reduction in the amount of radium used.

A careful record was kept of the amount

TABLE II
SQUAMOUS CELL CARCINOMA OF THE CERVIX
POLICY OF RADIATION THERAPY

Stage	Radium (mg. hr.)	Roentgen Rays (rads)
IA	8,000-11,000	None
IB	8,000-11,000	3,000-4,000 to parametrium
IIA	5,500-6,500	3,000-4,000 to parametrium
IIB	5,500-6,500	4,000 to whole pelvis
IIIA	4,000-5,000	6,000 to whole pelvis
IIIB	2,000-3,000	7,000 to whole pelvis

TABLE III
CANCER OF THE CERVIX
END RESULTS BY MODIFIED LIFE TABLE METHOD

Stage		Per Cent Surviving at Year						
		1	2	3	4	5	6	7
I	Study Group	100.0	96.6	86.1	86.1	86.1	86.1	86.1
I	Control Group	100.0	100.0	97.1	93.3	93.3	93.3	93.3
IIA	Study Group	94.8	84.6	84.6	76.9	76.7	76.9	
IIA	Control Group	97.4	92.3	89.5	89.5	89.5	89.5	89.5
IIB	Study Group	92.0	84.0	71.7	71.7	53.7	53.7	
IIB	Control Group	85.7	75.0	71.3	62.4	62.4	62.4	62.4
IIIA	Study Group	78.2	69.5	64.9	53.6	53.6	53.6	53.6
IIIA	Control Group	85.7	64.2	53.5	40.7	32.5	32.5	
IIIB	Study Group	84.0	68.0	63.9	54.4	54.4	54.4	
IIIB	Control Group	82.9	62.9	62.9	62.9	62.9	62.9	

of radiation given to the tissues to be excised by lymphadenectomy to enable definitive evaluation in further studies. When the radium is located high within the pelvis, the obturator lymph nodes receive about 1,000 rads from each 4,000 mg. hr. of intracavitary radium. One-half to one-third of that dose is delivered to the more distant external iliac and hypogastric lymph nodes.

The dose to the lymph nodes in each stage is summarized as follows:

Stages IB and IIA: Roentgen therapy contributes 3,000 to 4,000 rads and radium contributes 1,000 to 2,500 rads or a total of 4,000 to 6,500 rads in an over-all time of 5 to 6 weeks.

Stage IIB: Roentgen therapy contributes 4,000 rads and radium 750 to 1,200 rads in 5 to 6 weeks.

Stages IIIA and IIIB: External roentgen therapy, almost exclusively, contributes from 6,000 to 7,000 rads in a period of 6 to 7 weeks.

SURGICAL TECHNIQUE

Lymphadenectomy is performed 6 weeks after completion of irradiation. This has been determined as the optimum time in which to permit radiation changes within the cells and to allow for the easiest resec-

tion of tissue. A transabdominal approach with a midline incision is employed to open the abdominal cavity. After palpation and close examination of the abdomen for metastasis, the lower aortic area is exposed and one or more of the most prominent periaortic lymph nodes are excised. Regardless of whether this specimen was positive or negative, bilateral pelvic lymphadenectomy is performed. The lower common iliac, external iliac, hypogastric and obturator fossa lymph nodes with their surrounding fibrofatty tissue are excised. The dissection is carried from the level where the ureter crosses the common iliac artery to the inguinal ligament. The region of the cervix, the irradiated central portion of the primary growth, is not disturbed. Inoperability caused by radiation fibrosis is observed rarely. A clean dissection of the large pelvic vessels is done even when fibrosis exists; therefore, it is doubtful that radiation-induced fibrosis impairs the thoroughness of the lymphadenectomy.

RESULTS

Improvement in survival rates was the criterion for the first phase of the analysis (Table III). Modified life table survival figures were computed for each group, and

TABLE IV
CANCER OF THE CERVIX
FIVE YEAR SURVIVAL BY MODIFIED
LIFE TABLE METHOD

Stage	Study Group		Control Group	
	No.	Survived	No.	Survived
I	30	86%	39	93%
IIA	39	77%	39	89%
IIB	25	54%	28	62%
IIIA	23	54%	28	33%
IIIB	25	54%	35	63%
	142		169	

comparative descending survival curves were drawn.⁴ The lymphadenectomy group and the control group, for all stages combined, were found to be nearly identical in survival time. The curves for the different stages differed only slightly and showed a somewhat more favorable prognosis for the control group than for the lymphadenectomy group, though the differences were not significant (Table IV). The exception to this was in Stage IIIA, in which patients who underwent lymphadenectomy lived

longer than the controls. Of all the curves, the difference in this group was most pronounced, though still not significantly different statistically.

Statistically, according to random selection and stratification by stage of disease, the possibility of dying of causes other than cancer should be distributed equally between the study and control groups. Additional risks from surgical intervention would occur only in the lymphadenectomy group. All deaths were studied carefully to determine the cause. Table V gives the findings. The most frequent cause of death was recurrent cancer. Death from a second primary or from unrelated diseases occurred less often. Deaths from complications occurred in 8 instances in the lymphadenectomy group, and in 1 instance from radionecrosis alone in the control group.

The most common surgical complication was fluid accumulation at the dissection site^{3,8} (Table VI). This lymphocyst created pressure on the pelvic wall vessels and distorted the ureter's normal course. Leg edema and ureteral obstruction were the most frequent sequelae. In some instances, infection of the cyst contents resulted in a

TABLE V
CANCER OF THE CERVIX
CAUSE OF DEATH BY STAGE

Stage		Of Cancer	Other Primary	Intercurrent Disease	Complications
I	Study Group	1	1	—	2
I	Control Group	—	1	1	—
IIA	Study Group	6	1	—	1
IIA	Control Group	3	1	—	—
IIB	Study Group	7	1	—	1
IIB	Control Group	8	—	2	—
IIIA	Study Group	8	—	1	2
IIIA	Control Group	14	—	2	1
IIIB	Study Group	8	—	1	2
IIIB	Control Group	10	1	2	—
Total	Study Group	30	3	2	8
Total	Control Group	35	3	7	1

serious intractable pelvic wall abscess. Such abscesses were resistant to healing because of radiation damage of the tissue. Reduction of the cyst and of obstruction to the lower extremity relieved the obstructed ureters; however, kidney damage may have occurred in the interim.

If such complications could be prevented, the survival curves might be different and show more favorable results for the lymphadenectomy group. However, at present, these complications are inherent to this combined therapy procedure. One would hesitate to reduce the radiation dose in order that the patient might better tolerate the lymphadenectomy, since the low incidence of positive lymph nodes found in the surgical specimens indicates the value of radiation therapy (Table VI).

DISCUSSION

As gynecologists and radiotherapists, we have continued to search for combined therapies which would augment one another and produce the maximum benefit with a minimum of complications. Criteria for success of such combinations are simple: the combined therapy must produce a higher rate of cures than any one mode of therapy alone, and the benefits derived from it must offset any undesirable side effects.

There is an increasing number of reports in the medical literature on the results of treatment combining radiation therapy with hysterectomy; radiation therapy with hysterectomy and lymphadenectomy; and radiation therapy with lymphadenectomy alone. The high incidence of urinary tract fistulae and vaginal vault slough precipitated by intense irradiation and extended hysterectomy renders the first procedure prohibitive. This is especially true following central irradiation over the bladder, ureters and rectum. It appears that the only way the extended hysterectomy could be employed without excessive complications would be by reducing the amount of radiation given prior to the operation. We were reluctant to sacrifice the known bene-

TABLE VI
CANCER OF THE CERVIX
COMPLICATIONS

Lymphocyst		54
severe	20	
moderate	15	
mild	19	
Leg Edema		8
Hydronephrosis		14

fits of radiation therapy for an uncertain gain from the two methods combined. As an alternate approach, lymph nodes were extirpated rather than the primary lesion.

From 1954 to 1962, more than 450 pelvic lymphadenectomies were performed in our institution as part of the management of carcinoma of the cervix, providing the material for several different studies. From 1957 to 1960, 142 of these were in the clinical trial. The decision to prescribe the operation was always based upon the belief that additional benefit would be derived and that any complication from the operation would be minimal. The randomized trial results confirmed the clinical impression gained from analysis of earlier material that prognosis was not always enhanced by adjunctive lymphadenectomy. There was no difference in the results of treatment with or without adjunctive lymphadenectomy. Table v shows that there were 5 more dead from disease in the group without lymphadenectomy than in the group which had adjunctive surgery; 8 who had surgery died of complications so that both groups were about equal.

Failure of this operation to result in cure may be explained by the distribution of the cancer beyond the range of the operative site. Of the 100 patients in the previous study of Stage III only, 21 had positive lymph nodes situated within the pelvic area; 5 had positive lymph nodes above the pelvis and beyond the range of the lymphadenectomy. The remaining 7 patients had positive lymph nodes both within and outside the pelvis and the area they covered

TABLE VII
CANCER OF THE CERVIX
PATIENTS WITH POSITIVE LYMPH NODES

Stage	No. of Patients	No. of Positive Lymph Nodes	Per Cent
I	30	1	3.3
IIA	39	4	10.3
IIB	25	5	20.0
IIIA	23	4	17.4
IIIB	25	2	8.0
	142	16	11.3

was too extensive for complete removal.

The problem was not the same for all patients with positive lymph nodes. The number, the size, and the location of these positive lymph nodes were the determining factors in whether complete removal could be effected. In some patients, there was a large amount of metastatic spread throughout the multiple lymph node areas, often bilaterally. In others, the pattern was less diffuse, but the gross mass of metastatic cancer was large. These appeared as large single or matted multiple lymph nodes. Removal of the lymph nodes from about the large pelvic vessels by careful dissection was often done, but there seldom remained a sufficient margin of cancer-free tissue. So these patients were inoperable from the beginning.

In the random study under review, 16 patients of the 142 in the lymphadenectomy group had positive lymph nodes after radiation therapy (Table VII and Table VIII). Eight of these 16 had positive aortic lymph nodes outside the range of the dissection, and no cure from lymphadenectomy could be expected for these patients. Of the 8 patients who had positive lymph nodes situated within the pelvis, 3 had bilateral positive lymph nodes; no cures were obtained within this group. In the earlier survey, of 21 patients who had positive lymph nodes remaining after a full course of radiation therapy, 12 had metastases beyond the range of lymphadenectomy.

Observations on the usefulness of the lymphadenectomy would be incomplete if only patients with positive lymph nodes were studied. In all cases the operative specimen included a near *en bloc* mass of fibroadipose tissue containing lymph nodes of various sizes. Two sections were prepared of each lymph node extracted from the specimen. Some of these lymph nodes are so infinitesimal in size that they can easily escape detection. There is definite experimental evidence that microscopic disease is more radiosensitive and is destroyed by a smaller dose. Microscopic lymph channels connecting these lymph nodes may also be the site for metastatic cancer; they are often not included in the slide sections undergoing study and so are undetected.

SUMMARY

At The University of Texas M. D. Anderson Hospital and Tumor Institute, a clinical trial to investigate the benefits of pelvic lymphadenectomy after a full course of radiation therapy was begun in 1957 and completed in 1960. By a plan of randomization, 142 patients were entered, stratified by stage of disease, in the lymphadenectomy group and 169 in the control group treated by radiation therapy alone. There was approximately equal distribution in Stages I through III. Comparison by survival curves shows no significant improve-

TABLE VIII
CANCER OF THE CERVIX
POSITIVE LYMPH NODE SITES

Site	No. of Patients
Pelvis	8
Right	2
Left	3
Right and Left	3
Above Pelvis	8
Aorta	5
Right Aorta	1
Left Aorta	1
Right and Left Aorta	1

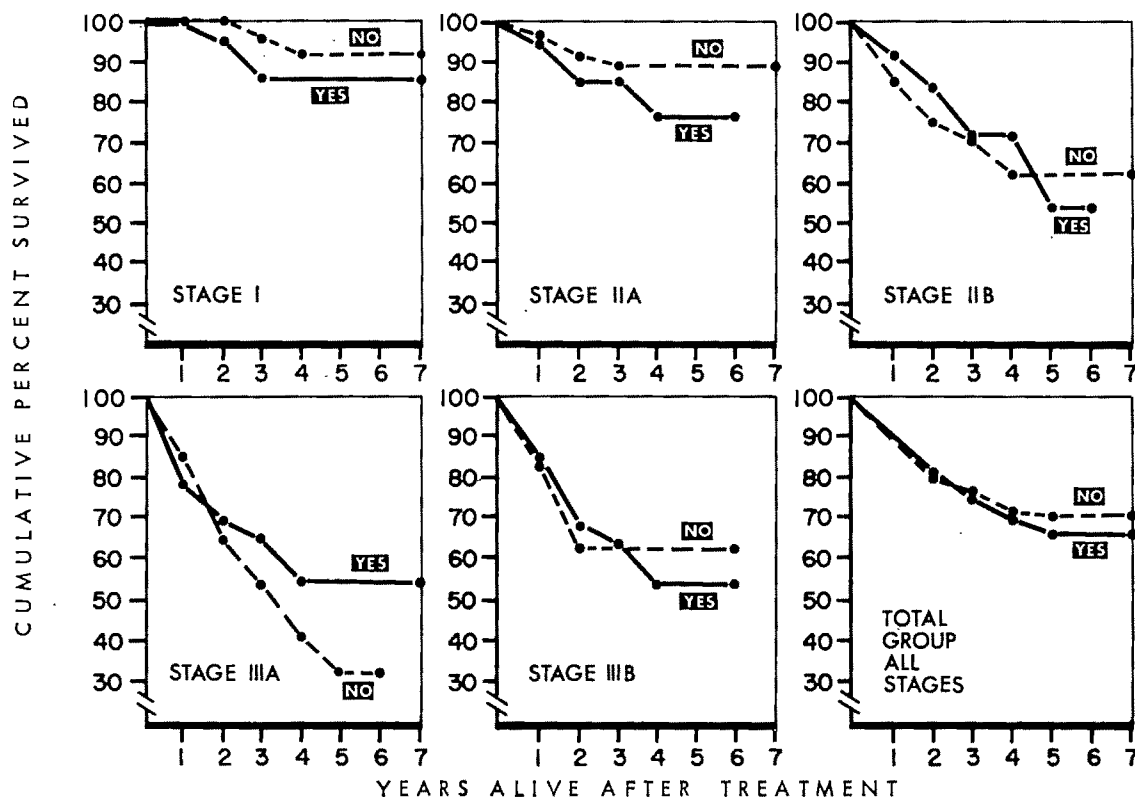


FIG. 1. Survival curves of patients treated for squamous cell carcinoma of the cervix. Curves for Stage I, IIA, IIB, IIIA and IIIB and all stages combined are shown. Patients who had lymphadenectomy added to their treatment are represented by solid line curves. The broken line curves are for patients who had radiation treatment only.

ment for those patients who had lymphadenectomy after radiation therapy (Fig. 1). There were, however, fewer deaths from recurrent cancer among the lymphadenectomy group and more deaths from complications. None of the patients with positive lymph nodes survived.

Postoperative complications developing in the dissection site were frequent and severe. Methods to prevent these complications may yet be developed. If this occurs, the combined therapy should be re-evaluated. Until then, we will use this combination only for specific needs and not as a routine adjunct to therapy.

It is suggested that greater attention be given to the lymph nodes in the area of the abdominal aorta. Systematic sampling of these lymph nodes, as part of the study of lymph node metastasis, will show a sur-

prisingly high incidence of positive lymph nodes.

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Note: Kolmogorov-Smirnov Significance Test. Since the modified life table method is essentially a nonparametric procedure, the t-test is not applicable as a measure of significance. The nonparametric Kolmogorov-Smirnov two-sample test was used to test for significant differences between those who had lymphadenectomies and their controls by stage. The test uses the difference between cumulative percentages. At no point was there a difference between the cumulative survival rates or percentages that equaled or exceeded the corresponding critical percentage needed for significance. The greatest difference found (Stage IIIA) was 21, and for a sample size of 28 at the 5

per cent level of significance, a difference of 37 would be needed.⁹

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"SUPPRESSIVE" CHEMOTHERAPY IN BRONCHOGENIC CARCINOMA *

A RANDOMIZED PROSPECTIVE CLINICAL TRIAL

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FOR the purpose of this paper, the term "suppressive" chemotherapy in the management of malignant disease is specifically defined as—"the regular (usually daily) administration of an anti-neoplastic drug over a prolonged and indefinite period of time (months or years) to patients who have recently received primary 'radical' treatment and have no objective evidence of tumor activity, but in whom the presence of subclinical active neoplasm, residual or metastatic, is strongly suspected." As the term "suppressive" implies, the treatment aims at *diminishing the rate of progress* of subclinical malignancy (in the primary region or in micro-metastases) and thereby prolonging useful, active life. Suppressive chemotherapy is somewhat different in concept to adjuvant chemotherapy which is generally employed as an *acute* course of drug treatment given to supplement radical cancer therapy in order to "deal" with microscopic tumor foci and thereby improve over-all results and survival. Suppressive chemotherapy is independent of the form or nature of the primary treatment and is not in any sense for radiosensitization. It is neither palliative nor "prophylactic." Suppressive chemotherapy assumes the presence of subclinical tumor activity (residual or metastatic) and acknowledges the likelihood of a fatal outcome; all it seeks to accomplish is a retardation of the process of neoplasia (Fig. 1).

Suppressive chemotherapy, if it can be achieved, has interesting implications. The traditional radical concepts of "extirpation" or "radiation sterilization" in the therapy of primary cancer, in spite of their emotional appeal, are not always relevant to tumor control, particularly in bronchogenic carcinoma. If rapidly growing tumors can, by some subtle means, be "curbed" and trained to grow slowly, much might be accomplished in clinical cancer therapy without recourse to crude destructive local measures. It is well known that many slowly growing tumors are compatible with prolonged survival and little morbidity. At the present time, the idea of slowing the growth of tumors (perhaps by inducing differentiation in cancer cells) is still a little fanciful, but may be potentially more fruitful than the purely ablative concepts currently preached and practiced. Partial and temporary tumor restraint is almost certainly the mechanism for some of the beneficial effects of hormone manipulation in breast cancer⁴¹ and in certain other "hormone dependent" tumors, such as prostate and thyroid neoplasms.

Considered in relation to bronchogenic carcinoma, the validity of the concept of suppressive chemotherapy can be tested using an alkylating agent. The following crucial question can be formulated: "In patients with clinically localized carcinoma of the bronchus, in whom surgical treatment is not possible or is inadequate, and

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who are treated with "radical" radiation therapy, are there advantages to be gained by immediately instituting long-term "suppressive" chemotherapy (with an alkylating agent) and continuing this treatment indefinitely?" The question can be broken down, specified and qualified by rigid definitions (see below). Some hypotheses can be developed.

HYPOTHESES

Postradiation suppressive chemotherapy (to be defined and used in a specified fashion): (1) *increases the survival time* in a certain (defined) group of patients with bronchogenic carcinoma; (2) *increases the*

quality of survival in this same group of patients (parameters to be defined); (3) *alters the course of disease* in these patients by affecting the evolution and pattern of distant metastases; (4) *is of greater value for undifferentiated or anaplastic tumors* than for squamous cell carcinomas; and (5) *is easy to control and free from significant risks or undesirable side effects*.

The study which forms the substance of this report was devised as a prospective randomized clinical trial^{40,64} specifically designed to test these hypotheses. Preliminary results show that hypotheses 1, 4 and 5 have been substantiated. Hypotheses 2 and 3 are unproven. The study is still in

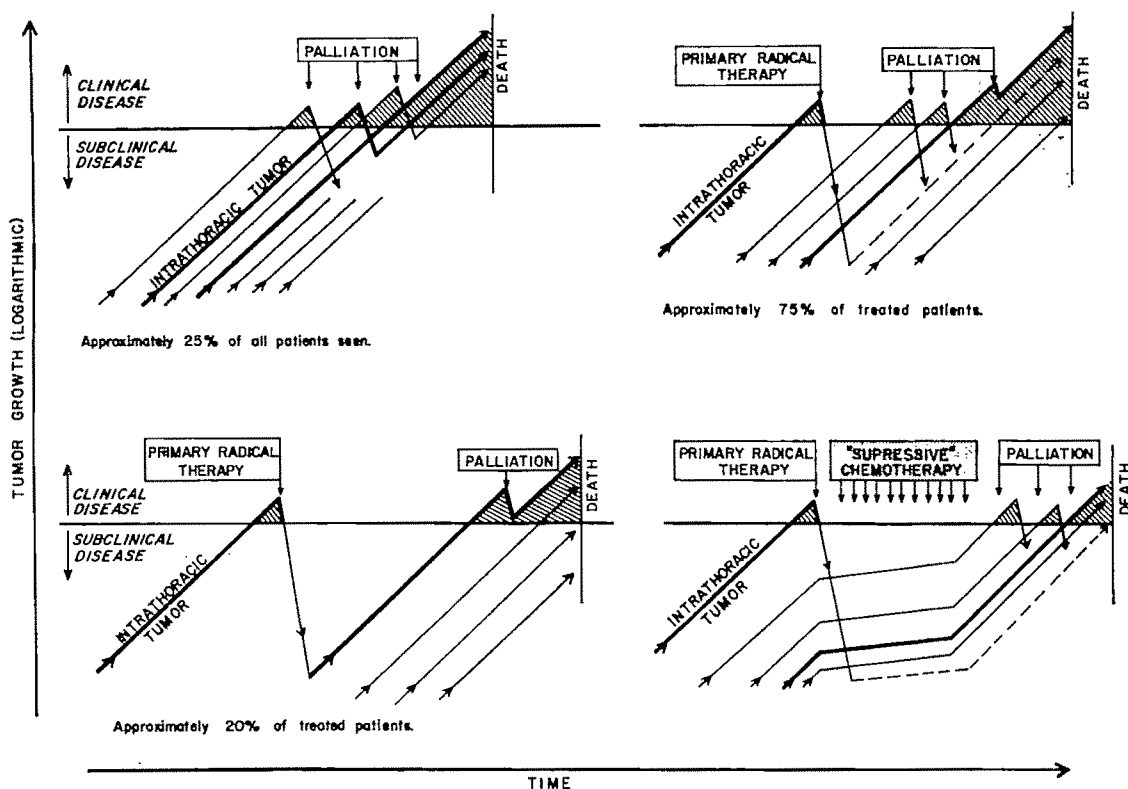


FIG. 1. Diagrammatic models of the clinical patterns and evolution of bronchogenic carcinoma. The horizontal line in each case represents the clinical threshold. Above the line are denoted symptoms and signs of tumor activity. Tumor growth (ordinate) is represented logarithmically. Time (abscissa) is shown linearly on an arbitrary scale. *Top left:* Distant metastases at first presentation. *Bottom left:* Partial control of primary tumor with local recurrence and extension later. Distant metastases are not a clinical problem. *Top right:* This is the commonest pattern. The primary tumor is controlled but distant metastases (present but occult at the time of primary radical therapy) are responsible for a fatal outcome. *Bottom right:* Theoretic mode of action of suppressive chemotherapy—the rate of growth is altered and the clinical manifestations of metastases or recurrence are delayed.

progress and will take another year or two to complete, but statistically significant results are now available. Additional and more detailed analyses will be possible at a later time.

FACILITIES, MATERIALS AND DEFINITIONS THE INSTITUTION

The study was undertaken at the Cincinnati General Hospital—the main teaching hospital of the University of Cincinnati College of Medicine. The hospital caters to the indigent of the City of Cincinnati (which has a total population of approximately 500,000 persons) but *not* to impecunious persons residing in surrounding municipalities, suburbs and county areas. The whole geographical complex known as the Greater Cincinnati Area has a population of about one million people, for whom the Cincinnati General Hospital provides emergency and accident services. Routine general medical care is only provided, however, for a total of between 90,000 and 100,000 City of Cincinnati indigents, about 50 per cent of whom are Negro. The derivation (on a yearly basis) of the clinical material used in the trial in relation to the over-all occurrence of lung cancer in the general geographical area is shown in Figure 2. Two-thirds of the patients to be discussed were in the lowest economic groups (receiving financial support from various welfare agencies) and were unable to contribute anything towards their hospitalization or treatment. One-fifth of the patients had very small incomes and were considered able to pay a nominal charge for clinic visits, and scaled-down charges for x-ray examinations, drugs, etc.

All patients to be described in this report were hospitalized initially, diagnosed and treated (surgery, radiotherapy, chemotherapy and terminal care) at Cincinnati General Hospital. There was no reason to doubt the accuracy of the diagnosis^{37,61} in any of the cases entered into the trial. All cases were referred from the Departments of Medicine and Surgery. Normally, the

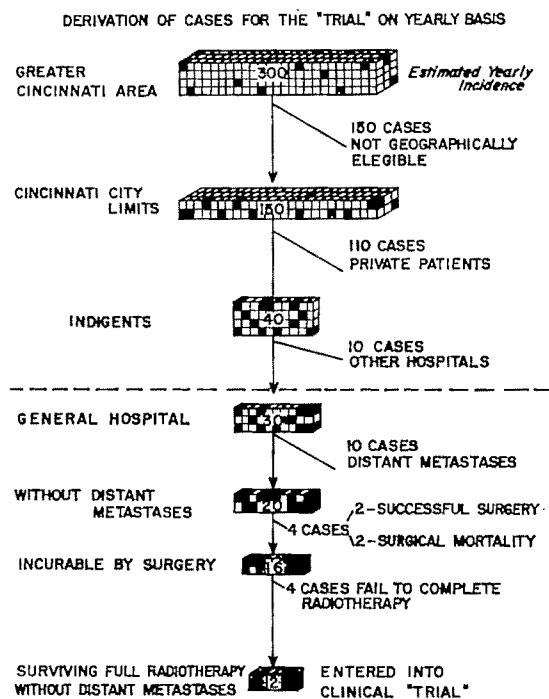


FIG. 2. It is estimated that the incidence of bronchogenic carcinoma in the Greater Cincinnati Area is about 300 new cases per year. The illustration explains why only about 12 cases per year are available for the chemotherapy trial. (The figures indicated are very close approximations.)

resident staff assumes the bulk of the responsibility for patient care, but patients accepted for the clinical trial to be described were managed in every detail by senior staff members (H.H., T.L.W., and H.P.).

THE PATIENTS

In order to be entered into the trial, the patients had to meet certain clinical and general criteria. Age, sex and race, which were *not* determining factors, are summarized in Table I and Figure 3.

Clinical and Histologic Grouping. The six clinical groups (A-F) which were accepted for the trial are defined in Table II. No particular prognostic significance is attached to this system of grouping. The specification is mainly on a gross anatomic basis and is simply used to describe the material entering the trial. Histologic proof was required and the designations "squamous cell," "oat cell," "anaplastic"

TABLE I
LUNG CARCINOMA—CINCINNATI GENERAL HOSPITAL
(DECEMBER 1961—JUNE 1964)
SEX AND RACE DISTRIBUTION

	All Patients	"Trial" Patients
Male	74 (88%)	28 (93%)
Female	11 (12%)	2 (7%)
White	46 (54%)	13 (43%)
Negro	39 (46%)	17 (57%)
Total	85	30

or "undifferentiated" were acceptable. All other designations (including "adenocarcinoma" and "alveolar cell" carcinoma) were disqualifying. In a few cases, histologic proof was not available initially (*i.e.*, superior vena caval obstruction) but was obtained subsequently. Histology did not effect grouping nor did it influence management of the patients once they were selected for the study (Table III).

General Qualifications. In the general run of patient material, it was unusual for

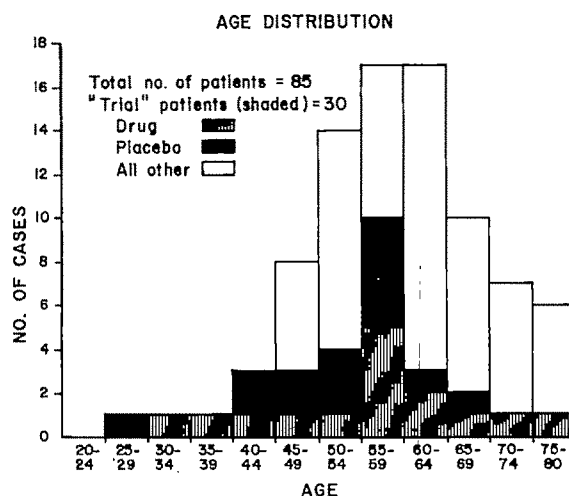


FIG. 3. Age distribution of all lung cancer patients diagnosed at Cincinnati General Hospital from December, 1961 to June, 1964. The age distribution of the drug and placebo cases is indicated.

carcinoma of the lung to develop "out of the blue" in otherwise healthy individuals (19 per cent of all cases). The level of morbidity due to diseases other than lung cancer was high, indeed many patients were harboring multiple pathologic proc-

TABLE II
CLINICAL GROUPING OF CASES ENTERING CHEMOTHERAPY TRIAL

	Chloram-bucil	Placebo	Total
Group A Found inoperable at thoractomy. No procedure other than biopsy	3	5	8
Group B Resection undertaken. Malignant disease known to be left within chest	3	2	5
Group C Inoperable because of location or local extension of disease (<i>i.e.</i> , extension into the mediastinum or contiguous bone involvement or pleural effusion)	2	1	3
Group D Inoperable because of age, coexisting disease or poor general condition	2	2	4
Group E Superior vena caval syndrome (primary presentation)	1	1	2
Group F Clinically involved or pathologically proved supra-clavicular lymph node metastases. No evidence of metastases beyond this area	4	4	8
Total	15	15	30

TABLE III
CLASSIFICATION BY HISTOLOGY

	All 85 Patients (including trial patients)	Trial Patients		
		Drug	Placebo	Total
Squamous Carcinoma	37 (43%)	8	7	15 (50%)
Undifferentiated Carcinoma Including "Oat-Cell" and "Anaplastic Cell"	45 (53%)	7	8	15 (50%)
Adenocarcinoma	3 (4%)	0	0	0

Percentages are approximate.

esses (Table IV). Only 38 per cent of lung cancer patients had an entirely negative past history of chest disease. The presence of other chronic diseases, pulmonary, nonpulmonary or psychiatric, did not in general disqualify patients from the trial unless these diseases were so severely disabling that they precluded the administration of a full course of radiation therapy or made out-patient management impossible. It was required that primary treatment for the lung neoplasm be initiated as soon as possible after diagnosis, and that the patient complete primary or postoperative radiotherapy without showing evidence of metastases beyond the irradiated areas.

During a 2½ year period, December, 1961 to June, 1964, a total of 85 new cases of bronchogenic carcinoma were seen at Cincinnati General Hospital. A breakdown of this material is shown in Figure 4. It can be seen that in roughly 25 per cent of

all cases either the disease was widely disseminated when the diagnosis was made, or the diagnosis was made at autopsy. In a further 25 per cent (approximately) of all cases, thoracotomy was considered justifiable, but in only 5 cases (1 in 4 thoracotomies) was a satisfactory grossly complete resection possible. The remaining 50 per cent of all cases were judged after full investigations and assessment to be unsuitable for surgical therapy for various reasons. The clinical groupings of cases which finally qualified for the trial are indicated by the lightly shaded areas in Figure 4.

A total of 30 cases entered the trial during the 2½ year period. The clinical course prior to the first therapeutic event is shown in Figure 5. Delay prior to therapy is broken into three components. Patient delay is seen to be very variable, depending as it does on imponderable factors. The

TABLE IV
SIGNIFICANT MORBIDITY UNRELATED TO LUNG CANCER IN TOTAL OF 85 PATIENTS

Pulmonary Diseases		Nonpulmonary Chronic Diseases	
None	32 (38%)	None	41 (48%)
Pneumonia (past history), Chronic Bronchitis, Tuberculosis, Bronchiectasis, Asthma, etc.	53 (62%)	Cardiovascular, Gastrointestinal, Genitourinary, Psychiatric, Neurologic, etc.	43 (52%)
No Significant Morbidity of Any Kind Apart from Lung Cancer		16 (19%)	

Percentages are approximate.

BREAKDOWN INTO CLINICAL GROUPS - 85 PATIENTS

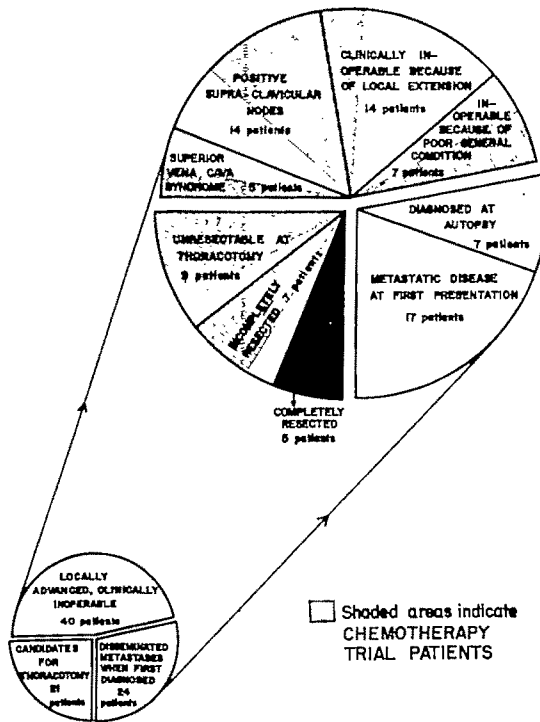


FIG. 4. Breakdown by clinical groups of all 85 cases of bronchogenic carcinoma diagnosed at Cincinnati General Hospital from December, 1961 to June, 1964. The term "metastatic" refers to distant (blood-borne) dissemination. A total of 30 of these patients qualified for the chemotherapy trial—their distribution among the clinical groups is indicated.

long periods between the initial consultation with a doctor and the establishment of the diagnosis in some of the cases is noteworthy. This delay was not entirely dependent on medical acumen; in some cases, patients, for reasons best known to themselves, failed to return for follow-up during diagnostic studies; in other cases, breakdowns occurred in communications, and patients, due to ignorance (or perhaps to temporary improvement in their symptoms), failing to appreciate the seriousness of their situations, did not report back to the clinic. Nonetheless, diagnostic delays greater than 2 months occurred in 8 of 30 cases. The "therapeutic delay" is harder to account for; it represents time spent deciding if to treat, how to treat, whether to

operate, persuading the patient, obtaining further diagnostic studies, etc. This type of delay has been noted by others (Krant *et al.*²³), who observed what they called a "lag time" of the order of 28 days (median value) between diagnosis and the start of therapy. The urgency of the situation in the mind of the clinician may in these circumstances have been dictated by severity of symptoms. The actual *causes* of delay are irrelevant to the biologic process of neoplasia; delay for whatever reason, be-

REPRESENTATION OF CLINICAL COURSE PRIOR TO FIRST THERAPEUTIC EVENT IN "TRIAL" PATIENTS

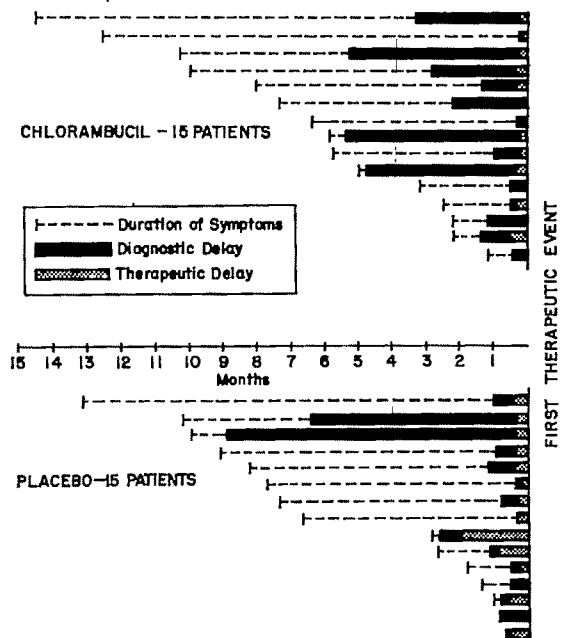


FIG. 5. The 30 trial patients shown, by their process of selection, represent "advanced" disease at the time of initial therapy. The cases are arranged in a descending order of magnitude of total pre-therapeutic delay. It can be seen that patient delay contributed mostly to the over-all time prior to treatment, but that there was considerable variability. The solid black bars represent intervals between the time when medical aid was first sought and the time that the diagnosis was established. The stippled areas represent delay after the diagnosis had been made (see text). All times are measured relative to the "first therapeutic event." There was no correlation between the length of the pre-therapeutic period and the length of survival in the entire group of cases studied (correlation coefficient 0.19).

cause it allows the disease to proceed unchecked, is theoretically undesirable, but when therapy has little to offer, reluctance to add further burdens to the patient is understandable. In the cases studied, overall delay as measured by mean or median estimates prior to the first therapeutic event, although by chance slightly greater in drug (chlorambucil) patients than in controls, was not statistically significant (Fig. 8).

TREATMENT

Radical Radiation Therapy. This was conceived as the initial primary "radical" treatment whether or not it was used after incomplete or unsuccessful surgery, and was designed as an attempt to control adequately all the overt neoplastic disease. A cobalt 60 teletherapy unit (80 cm. source skin distance) was used to deliver a tumor dose of 5,000 r in 4 to 5 weeks to the intrathoracic lesion (primary plus mediastinum) and also to both supraclavicular areas if either or both were clinically or histologically involved (Group F cases). The radiation technique consisted of generous anterior and posterior ports, adequate to cover the roentgenologic lesion and adjacent mediastinum. Portal sizes varied a little from case to case. When supraclavicular areas were also treated, a single large anterior port, usually 10×20 cm., was used with a suitable shield for a central 3 cm. wide strip to protect the trachea, esophagus and cord. In Group C cases where pleural effusion was a presenting feature, nitrogen mustard (0.4 mg./kg. of body weight) was given intrapleurally as part of the initial radical therapy in addition to the standard course of irradiation.

Suppressive Chemotherapy. The drug chosen for the trial was chlorambucil. There was no compelling reason for this particular choice, but there is some basis for the use of an alkylating agent, since nitrogen mustard is known to have a palliative value in some circumstances in bronchogenic carcinoma (see discussion). Chlorambucil is a good representative of the oral alkylating agents,

its dosage is easy to regulate, and it is a familiar drug in every-day clinical use. The toxicity of chlorambucil, when used in moderation, is virtually confined to bone marrow depression; it does not usually give rise to other unpleasant toxic effects such as gastrointestinal disturbances, hemorrhagic cystitis, epilation, etc. It is emphasized that the study was not designed to evaluate any particular drug, but rather to *investigate the validity of the concept of "suppressive" chemotherapy.*

Treatment with chlorambucil was started as soon as possible after the end of radiotherapy. The dosage used was between 2 and 8 mg. per day, by mouth, adjusted in order to maintain the total white blood cell count at a level of about 2,000 to 4,000 per cu. mm. over an indefinite period of time (or until the trial was terminated for any particular case). Significant thrombocytopenia was not observed in our series, but had it occurred before leukopenia, the dosage of chlorambucil would have been gauged on the platelet count rather than the white blood cell count with a view to maintaining the platelet count above 100,000 per cu. mm.

PROCEDURE

Patients are initially placed in one of the six clinical groups (A-F). Histologic type is noted but does not affect grouping. Cases from each group are randomly assigned to chemotherapy or placebo (controls). All patients attend the chemotherapy clinic weekly starting 2 to 3 weeks after the commencement of radiotherapy. Preliminary history taking, recording of physical findings and the starting of code sheets are accomplished. Weekly blood cell counts are instituted. At the end of radiation therapy, or shortly thereafter, medication (chlorambucil or placebo) is started and the dosage of the former is adjusted according to the white blood cell count. Both treatment and control patients are handled in an exactly similar fashion; the placebo tablets used have an appearance indistinguishable from that of chlorambucil tablets (Leukeran-

Burroughs Wellcome), but the trial is not "double-blind," since chlorambucil-induced leukopenia is a guide to management.

The chlorambucil or placebo therapy is terminated in each case at the time that a definite clinical diagnosis of local intrathoracic recurrence or distant metastasis can be made. Evidence of tumor activity within the chest, such as the development of superior vena caval obstruction, esophageal obstruction or fistula, pericardial effusion, pleural effusion with malignant cytology, or any other complication unquestionably due to neoplasm, is a reason for stopping medication. The manifestations of distant metastatic disease are not generally difficult to recognize and give a fairly clear-cut end point. Periodic routine roentgenographic studies and, occasionally, liver and brain radioisotope scans are helpful in reaching a diagnosis of metastatic disease. The diagnosis of recurrence or metastasis is interpreted as indicating a loss of control or loss of suppressive effect on the neoplasm by the chemotherapeutic agent.* Cases removed from the trial are followed and supervised indefinitely in the clinic or in the wards of the hospital. The best available symptomatic treatment is given for each specific problem as it arises. Hospitalization is arranged for terminal care. Autopsies are obtained in as many cases as possible (Table v).

PARAMETERS

In order to test the five hypotheses set up at the beginning of this paper, the following five sets of parameters were used.

Hypothesis 1—Survival. This was measured in each case from several different time points and the data were analyzed by three different statistical techniques. The time points used were:

(a) The *onset of symptoms* or "apparent

* It is now felt, after some experience with suppressive chemotherapy and some further consideration, that this interpretation is wrong (see *Discussion*). For the purposes of the trial, as designed and conducted, it did, however, provide a time point at which to terminate chlorambucil or placebo therapy.

TABLE V
AUTOPSY RATE

	All Patients	"Trial" Patients
Total Mortality Autopsies	75 48 (64%)	23 12 (52%)

clinical onset." The inherent inaccuracy of this time point is recognized, but special efforts were made to pinpoint it; this information was included in the data for the sake of completeness.

(b) The date *medical aid was sought*. This is the time that the patient first reports to a doctor complaining of symptoms relating to his bronchogenic carcinoma.

(c) The date of *diagnosis*. This is generally the date of histologic diagnosis and, therefore, may be the date of thoracotomy in some patients. In certain cases (*i.e.*, superior vena caval obstruction), it is the date of clinical diagnosis.

(d) The date of the *first therapeutic event*. This is sometimes a surgical procedure and sometimes the first day of radiation therapy.

(e) The *beginning of chemotherapy*. (Normally soon after the end of radiotherapy.)

(f) The date of *first clinical evidence of metastatic disease or recurrence*. Since patients attend the clinic weekly, this time point can be reasonably well fixed.

The most important time point from which to measure survival is taken to be the time of the *first therapeutic event*. This is the first occasion that any action is taken which could conceivably influence the course of the disease.

Hypothesis 2—Quality of Survival. Four separate parameters of quality of survival were employed:

(a) The performance status (Karnofsky *et al.*³²), which like other systems for quality estimation has imperfections, was considered to be a good general over-all index of quality of survival. The assessment was made weekly by an independent, unbiased observer (registered nurse) who was not

aware of the nature of the treatment in individual cases. During hospitalization, the assessment was made weekly by the head nurse in the ward. Although morbidity in lung cancer patients may be influenced somewhat by other coexisting chronic diseases and by intercurrent acute disorders, it can usually be directly or indirectly related to the clinical status of the malignant process. Carcinoma of the lung, after all, is a pernicious and sinister process and its manifestations tend to overshadow those due to other lesser maladies.

(b) Total duration of hospitalization. This is a somewhat crude measure of gross disability. It is evident that existence outside the hospital is of a higher "quality" than existence within the hospital and therefore the shorter the over-all period of hospitalization, the better for the patient.

(c) Weight change during the period of chemotherapy or placebo. Weight loss (related to original weight) is another somewhat crude measure of over-all quality of survival.

(d) The occurrence and/or persistence of chest symptoms during the period of chemotherapy or placebo. Chest symptoms were individually graded as "absent," "present" or "severe" and recorded weekly for each patient. An appraisal of the total morbidity due to symptomatic chest disease was thus obtained.

Hypothesis 3—Alterations in the Natural Course of the Disease. The time of onset, type and pattern of metastases were recorded in each case and comparisons were made between chlorambucil and placebo patients. Survival time after the appearance of recurrent or metastatic tumor was also studied. Autopsy information was available in more than half of the patients who succumbed (Table v). The small number of cases studied so far makes the testing of this hypothesis somewhat unsatisfactory.

Hypothesis 4—Histology in Relation to Suppressive Chemotherapy. Histologic types were compared to see if the concept of sup-

pressive chemotherapy is valid only for undifferentiated tumors. Those cases in which the words "squamous cell carcinoma" appeared on the pathology report were compared with all others grouped together ("anaplastic," "undifferentiated," "oat cell," etc.). A great deal of variability exists in histologic opinion, and bronchogenic carcinoma, like many other tumors, shows pleomorphism, allowing different histologic types to be discerned in different portions of the same tumor (Willis⁶²). These data, therefore, are presented with reservations.

Hypothesis 5—Drug Toxicity. The principal toxic effect of chlorambucil observed clinically is marrow depression leading to leukopenia and (rarely) thrombocytopenia. Weekly blood cell counts were performed in all cases. Other toxic effects were watched for, but none were seen.

COLLECTION AND ANALYSIS OF DATA

Data sheets were designed so that all information, expressed in digital form, was suitable for transfer to punch cards. Weekly flow sheets for weight, performance status, white blood cell count and drug dosage were used. Each of eight different chest symptoms was recorded in digital form as "absent," "present" or "severe" at each patient visit. At the conclusion of the trial, in each case, further information was added to the master code sheet. For each patient, the master code sheet was completed when all information (including autopsy data when available) was at hand. The data from each case were finally reduced to three IBM cards, with a view to making the compilations, tabulations and statistical analyses on the IBM 7040 computer at the University of Cincinnati Medical Computing Center. Only limited analyses have so far been attempted. Many additional breakdowns, tabulations and analyses will be possible when complete data are available on all of 38 cases now in the trial. Some of the mathematical work herein presented was in fact done "by hand."

TABLE VI
MEAN SURVIVAL (IN DAYS)—23 "TRIAL" PATIENTS DECEASED
WITHIN 15 MONTHS OF INITIAL TREATMENT

	Placebo Group (11 patients)		Chlorambucil Group (12 patients)		t	P
	Mean	S.E.	Mean	S.E.		
From Onset of Symptoms	307.75	40.74	406.67	38.44	1.77	<.05
From First Consultation	190.00	25.29	290.08	36.82	2.2	<.025
From Diagnosis	163.37	14.74	237.50	28.14	2.24	<.025
From First Therapeutic Event	147.91	16.06	229.83	27.78	2.49	<.025
From Beginning of Chemotherapy	105.64	14.86	180.08	27.60	2.31	<.025
From First Clinical Metastases	66.90	14.07	90.91	18.35	1.02	NS

RESULTS

SURVIVAL (HYPOTHESIS 1)

Survival for the trial patients was assessed in three different ways: mean survival, median survival and life table (actuarial) analysis. The data are summarized in Table VI and in Figures 6, 7, 8 and 9. It can be seen that in the patients who died within 15 months of the first therapeutic event (12 chlorambucil, 11 placebo), the mean survival measured from four different time points was significantly greater for chlorambucil cases ($P = <.025$). The median survival times from the first therapeutic event (for 12 chlorambucil and 12 control patients eligible to survive 1 year) was also significantly greater for chlorambucil cases ($P = <.001$). A plot of survival following the first therapeutic event, by life table (actuarial) method, shows that the chlorambucil and placebo lines separate after the first 3 months—the chlorambucil cases apparently doing better, but a high degree of statistical significance cannot be claimed by this last analysis. More cases and follow-up are needed.

QUALITY OF SURVIVAL (HYPOTHESIS 2)

It was not possible to demonstrate any real difference in quality of survival between chlorambucil and placebo cases by any of the four parameters used.

(a) The average performance status during the trial was computed separately for

both chlorambucil and placebo patients and was found to be almost identical (t test = 0.421, d.f. 28). Similarly, the performance status averaged out and time weighted over the whole period of survival, including the postchemotherapy period, was almost exactly the same in both groups (t test = 0.755, d.f. 14).

(b) The average total duration of hospitalization after the beginning of chemo-

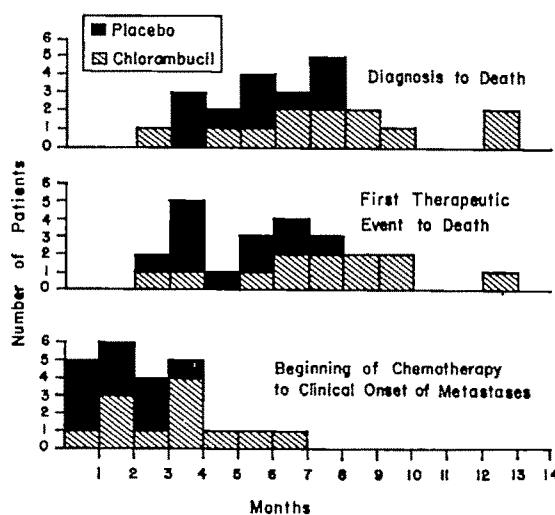
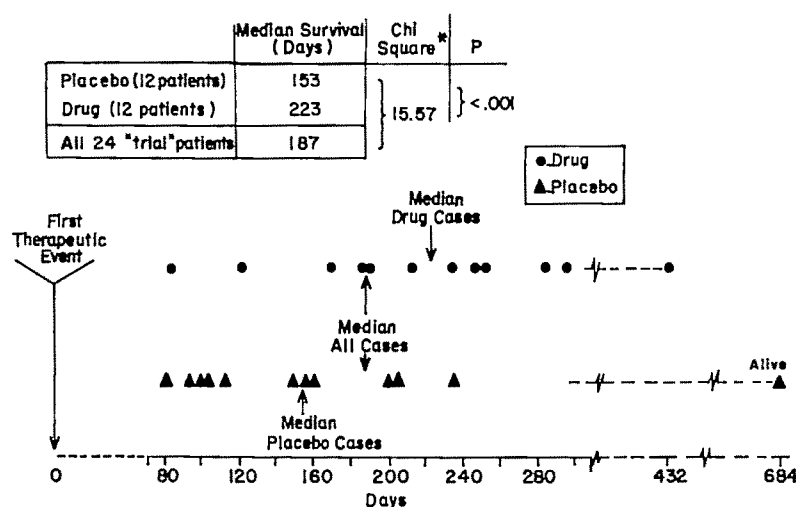


FIG. 6. There were 12 chlorambucil and 11 placebo patients who died within 15 months of the first therapeutic event. Survival is shown (to the nearest month) comparing the two groups of cases. It can be seen that, in general, the placebo cases tend to cluster to the left and the chlorambucil cases show a greater spread and extend more to the right.



* Median Test. Dixon, W.J. and Massey, F.J. "Introduction to Statistical Analysis", 2nd ed. McGraw-Hill, 1957

FIG. 7. Survival times for 24 trial patients eligible to have survived 1 year are represented as symbols along a time axis. The placebo cases tend to bunch up to the left, whereas the chlorambucil cases are more spread toward the right. The median survival time for each treatment group is compared with the median survival time for all cases combined. The statistical analysis and P value are given.

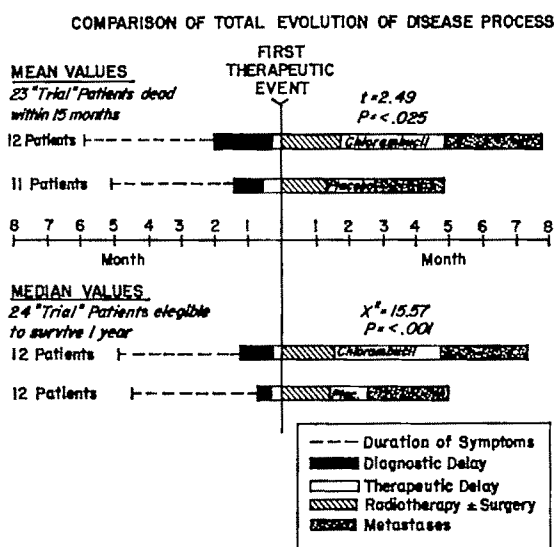


FIG. 8. This diagram summarizes mean and median survival data. All time periods, expressed as mean and as median values, are related to the "first therapeutic event" shown as a central vertical line. Total delay time (duration of symptoms plus "diagnostic delay" plus "therapeutic delay") shown to the left of the center line is not significantly different for chlorambucil or placebo patients. Similarly, the two time periods occupied by "Radiotherapy ± Surgery" and "Metastases" are not significantly different for the two treatments. The difference in the duration of chlorambucil or placebo therapy can be seen and the sta-

therapy or placebo was virtually identical for both groups (Table VII). Although the chlorambucil cases averaged about 4 days longer in the hospital, this may have been a reflection of their longer over-all survival.

(c) The weight change during the period of chemotherapy or placebo expressed as a percentage of original weight showed marked variability and was not consistently related to the over-all status of the disease. One or two patients actually gained some weight while deteriorating, and in one case cardiac decompensation and edema complicated the picture. It was not possible to draw any firm conclusions based on weight change; the over-all impression was of a predominant pattern of gradual weight loss during the course of the trial in both



tistical significance of this difference is indicated. The total mean duration of the whole course of the disease after the initiation of treatment is approximately 5 months for placebo cases and approximately 8 months for chlorambucil cases. The corresponding approximate median values are 5 months and 7½ months, respectively.

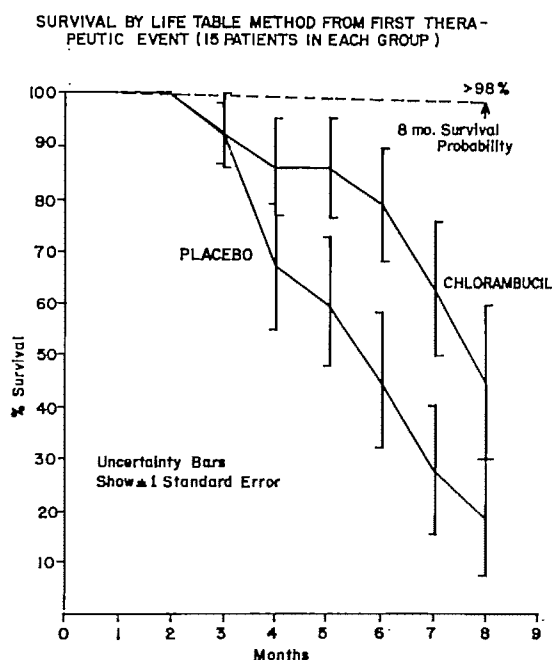


FIG. 9. The survival following the "first therapeutic event" is plotted for 15 chlorambucil and 15 placebo cases by the life table method.^{3,13,17,39} In some of the cases, follow-up was short and incomplete when this analysis was carried out. The standard errors of the survival rate were calculated by the method of Greenwood (see references 13, 16, 39). Since the numbers of cases were small and the follow-up short, this particular presentation of the data has limitations but it does show a separation of the two groups of cases. It is possible that the two lines when followed out sufficiently may converge (probably at about 1 year), suggesting that the effect of chlorambucil on survival occurs mainly for the short term cases.

groups of cases. No statistical analysis of these data was attempted.

(d) The frequency with which chest symptoms were present during the trial was compared for both chlorambucil and placebo cases. Noteworthy was the fact that the over-all incidence of chest symptoms (particularly cough and sputum) was high in both groups of patients. Although these symptoms were present, they were seldom severe or incapacitating (Table VIII). Cough and sputum were admitted in 80 to 90 per cent of all patient interviews. Chest pain, often related to a thoracotomy scar, was admitted in 40 to 60 per cent of

TABLE VII

MORBIDITY AS MEASURED BY TOTAL DURATION OF HOSPITALIZATION (IN WEEKS) FOLLOWING COMPLETION OF PRIMARY THERAPY

	Mean Duration of Hospitalization (in weeks)	Standard Error
All Patients	5.34	0.55
Drug Patients	4.47	0.76
Placebo Patients	3.87	0.56

such interviews. No statistical analysis of these data has been attempted, but the figures are presented for what they are worth. It is concluded that there has been little or no difference in chest symptomatology between chlorambucil and placebo patients.

The course of events for all trial patients after the start of therapy is shown in Figure 10. For the first month or two, the patients are either recovering after surgical procedures or enduring a harrowing course of radiation therapy, with its attendant local and general reactions. Sometimes, when radiotherapeutic insult is added to surgical injury, it may be 8 or 9 weeks or more before the patient, reeling after this combined onslaught, begins to recover a little of his equilibrium. He then enters the phase of "suppressive" treatment with drug or placebo. The need for weekly clinic attendance, with its distasteful little rituals of blood counting, interrogation and physical examination, creates and perpetuates in the patient a state of chronic invalidism and doctor-dependence, which persists until the next inevitable crisis—the clinical manifestations of recurrent or metastatic tumor. The period during which regular clinic attendance is imposed on the patient is a time of uneasiness and apprehension. Even though his symptoms may be mild, he is in fear that his doctor will, at any moment, discern some new and dreadful abnormality requiring further hospitalization or un-

TABLE IX
REASON FOR STOPPING "TRIAL"—25 PATIENTS

	No. of Patients			
	Drug	Placebo	Total	Per Cent
Local Recurrence within Chest (no evidence of distant metastases)	4	2	6	24
Distant Metastases Appearing at Various Sites Simultaneously	4	5	9	76
Distant Metastases Appearing Initially in Bone	3	2	5	
Distant Metastases Appearing Initially in Brain	2	1	3	
Distant Metastases Appearing Initially in Liver	1	0	1	
Distant Metastases Appearing Initially in Extrathoracic Lymph Nodes	0	1	1	

survival for these patients has been labored, it is emphasized that the general level of morbidity as measured in this study is no better and *no worse* for the chlorambucil cases as compared with placebo cases.

CHANGES IN THE COURSE OF THE
DISEASE (HYPOTHESIS 3)

In studying the evolution of disease in chlorambucil and placebo patients, no apparent difference in the pattern of development of metastases could be seen. The reasons for stopping the trial (discontinuing the medication) in 25 patients are summarized in Table IX. In about one-quarter of the cases, the trial was stopped for obvious recurrent tumor activity within

the thorax. In the rest, metastatic disease at various sites outside the chest required termination of the trial. The numbers are too small to draw any firm conclusions, but it would appear that the various manifestations of tumor activity studied are similar in both chlorambucil and placebo groups.

The disease pattern at death, as far as liver, brain, bone and "other" metastases were concerned, in 23 trial patients is shown in Table X and is compared with the disease pattern seen in another 52 cases who died during the same time period at Cincinnati General Hospital. Again, no real difference is apparent between chlorambucil and placebo cases, although the numbers are small and the observations recorded are

TABLE X
DISEASE PATTERN AT DEATH—75 PATIENTS*

	52 Non-trial Patients	23 "Trial" Patients		
		Placebo	Drug	Total
Blood Borne Metastases (various sites)	39 (75%)	9	7	16 (70%)
Liver Metastases	21 (40%)	4	4	8 (35%)
Brain Metastases	12 (23%)	3	2	5 (22%)
Bone Metastases	15 (29%)	6	3	9 (39%)
Other Metastases	31 (60%)	8	6	14 (61%)

* This table was compiled from autopsy information when available, and from clinical records. The incidence of metastases at various sites may therefore tend to be underestimated.

Percentages are approximate.

somewhat gross. The cause of death was directly related to neoplasm in all trial patients who died (Table XI). Of the 52 non-trial patients, 43 deaths were due directly to tumor, 5 to other causes and 4 to surgical mortality.

HISTOLOGY IN RELATION TO EFFECTIVENESS OF CHEMOTHERAPY (HYPOTHESIS 4)

It was possible to compare the median survival time in a total of 13 cases diagnosed as "undifferentiated" or "oat cell" carcinoma, 6 of which received placebo and 7 received chlorambucil. For the placebo group the median survival time was 159 days and for the chlorambucil group, 234 days. The difference is regarded as statistically significant ($P=.0379$). Of 12 cases diagnosed as "squamous cell carcinoma," 5 received placebo and 7 chlorambucil. The median survival for the placebo group was 148 days and for the chlorambucil group, 200 days. This was not considered a statistically significant difference ($P=.162$). More data will be available in due course to evaluate further this facet of the study.

DRUG TOXICITY (HYPOTHESIS 5)

No toxic effects of chlorambucil were seen. Leukopenia of the order of 2,000 total white blood cell count was frequently observed, but this never seemed to be associated with any difficulties or complications. Thrombocytopenia and other "side" effects

were not observed. It is assumed that chronic administration of chlorambucil must have produced some low grade cumulative marrow damage but there was no suggestion in any of the patients of clinical repercussions from this cause. It is concluded that the degree of marrow damage produced was insignificant for these patients.

DISCUSSION

THE LIMITATIONS OF RADICAL THERAPY

When the lung cancer process is viewed in its four dimensions, the overwhelming importance of *rate of growth* and tumor *transplantability* is readily perceived. These factors may indeed be interrelated. Studies based on modern concepts of exponential tumor growth⁵⁸ have been applied to primary lung cancer^{19,48,49,58} and have suggested that tumors which may appear clinically to be rapidly growing may have been preceded by surprisingly long pre-clinical phases. Garland *et al.*¹⁹ estimate that the doubling time for squamous and for undifferentiated lung tumors is in the region of 4 months, and that the over-all tumor "duration time" from inception to clinical recognition is some 10 to 15 years. This seemingly large estimate, based as it is on certain assumptions, may appear a little unrealistic (even far-fetched) and it may be argued, with justification, that there are certain

TABLE XI
PRIMARY CAUSE OF DEATH—75 PATIENTS

	All Non-trial Patients	"Trial" Patients
Death Directly Related to Neoplasm	43 (83%)	23 (100%)
Cerebrovascular Accident (8 months postpneumonectomy, no tumor at autopsy)	1	—
Cerebrovascular Accident (latent bronchogenic carcinoma at autopsy)	1	—
Confluent Lobular Bronchopneumonia (latent bronchogenic carcinoma at autopsy)	3	—
Surgical Mortality (21 thoracotomies)	4	—
Total Mortality	52	23

built-in fallacies and pitfalls inherent in the assessment of tumor growth rates and that variations in "host" resistance²⁵ must be taken into account. It must be further argued that estimates of 10 to 15 years tumor duration time are based on cases pre-selected because of their slow growth rate, and such estimates, therefore, do not represent the general or average picture of lung cancer. Notwithstanding these arguments, there is clearly a lesson to be learned. What is observed as the clinical syndrome of lung cancer must be regarded as only the brief and devastating climax to a prolonged, insidious, subclinical process which probably takes many years before it finally reaches the clinical threshold (Fig. 1).

If it is accepted that the pre-clinical course of the disease may be as much as 10 times as long as the clinical course, it is evident that there is ample opportunity for metastatic disease to establish itself long before the primary tumor gives rise to its first symptom. Indeed, it would be unrealistic to believe that bloodstream migration and distant colonization by tumor cells bear any temporal relationship to the somewhat arbitrary occasions of diagnosis and treatment. Collins,¹⁰ basing his argument on the observable growth rate of pulmonary metastases from bowel neoplasms, demonstrates in a plausible way that metastatic disease in distant sites can become established long before currently conceived diagnostic techniques could possibly detect the primary lesion. It follows, therefore, that, after the primary lesion is successfully ablated, the ultimate outcome will depend upon whether or not the patient survives long enough to succumb to metastatic disease. In tumors of slow growth rate, arguments for and against radical therapy for the primary tumor have little relevance to practical cancer management, since trouble arising from metastatic disease may be remote, and the primary lesion meanwhile requires urgent treatment. Therefore, if survival is to be a matter of years, the primary lesion should be thoroughly and carefully treated to prevent recurrence. When, however, the clinical

cancer process is telescoped into a matter of a few short months (such as it usually is in bronchogenic carcinoma), the wisdom of imposing on the patient debilitating and sometimes prolonged ablative treatment is questionable.

In the trial described in this paper, "radical" radiation therapy was administered. The basic concept underlying this approach was that radical radiation therapy would give long term control of the primary area and that suppressive chemotherapy would give similar long term control of subclinical metastatic disease. Now that the results have been analyzed, it is felt, in retrospect, that the radical radiotherapy given was probably unnecessary and that the same results might well have been achieved with an abbreviated and more concentrated course of irradiation. "Radical" is very much a relative term when applied to the radiotherapy of lung cancer, but there is no doubt that in some circumstances high dose localized irradiation can destroy primary bronchogenic carcinoma and lymph node metastases within the chest.^{5,6,7,57}

A study of the clinical evolution of the lung cancer process reveals two basic patterns^{20,21} (Fig. 1). These seem to be only loosely related to presenting clinical features or to histologic subgroups:

(1) *Localized type*. This represents about 20 per cent of all cases. The tumor remains confined to the chest throughout its entire course. It may involve hilar or mediastinal lymph nodes, but not extrathoracic lymph nodes. Blood-borne metastatic disease, if it occurs at all, is not of clinical significance. Some patients in this group (perhaps 50 per cent of them) survive for time periods over 1 year. It is from this group that the *few 5 year survivors* are drawn. These cases may correspond largely with the more slowly growing and less aggressive types described by Garland *et al.*¹⁹ in which positive roentgenographic findings can sometimes be discerned retrospectively 1 year or more prior to diagnosis.

(2) *Generalized type*. This represents about 80 per cent of all cases. The tumor is

generalized when the patient is first seen. In most cases (but not always) this dissemination is subclinical, but obvious extra-thoracic metastases declare themselves within a few weeks or months of the diagnosis. Nearly all of these patients are dead within 1 year. *None of these patients are ever "cured."* Karnofsky *et al.*³¹ and Golbey³⁰ recognize an additional subgroup within this main group which they designate "organ specific pattern." Here metastatic disease tends to dominate in one organ or system (*i.e.*, brain, liver, bone) rather than in many systems simultaneously. The importance of this subgroup is that the survival time may be a little better than in cases where the disease is more generalized, since successful treatment of the metastatic site (such as brain) may occasionally be followed by many months of trouble free survival. Radiation therapists are all familiar with occasional cases of this type.

The concept of these two groups immediately places a fundamental limitation on the potentialities of local radical therapy to "cure" the disease. If it were possible by vigorous combinations of surgery, irradiation and/or other means, to achieve complete elimination of the intrathoracic tumor in all cases treated, without significant morbidity or mortality, the very best obtainable over-all "cure" rate would be 20 per cent (all the cases biologically predetermined as "localized type"). All efforts directed at more efficacious treatment of the primary lesion (such as radiosensitization,⁴⁰ preoperative radiotherapy,^{5,6} etc.), desirable though they are, can only improve "cure" rates within that certain group of cases which comprises only about 20 per cent of the total clinical problem. This crucial point is seldom mentioned by those dedicated to the doctrine of an ever more efficient attack on the primary lesion.

It would be of great value to be able to recognize and differentiate the "localized" from the "generalized" groups at the time of diagnosis. Much futile effort could thereby be saved in clinical management, and much overzealous therapy and iatrogenic morbidity could be avoided. Fein-

stein¹⁸ approaches this problem in an original and unique way; by classifying and analyzing *symptoms*, he is able to divide patients into six groups. The 5 year survivorship can then be related to the groups, *irrespective of treatment*. Careful analysis of symptoms is a neglected approach to cancer prognosis and argues strongly for a degree of biologic predeterminism. It would appear that surgical operability criteria necessarily preselect those patients with a favorable prognosis, and that results may be more closely related to the biologic nature of the disease than to the treatment given. Another approach is that of Pillers *et al.*,⁴⁴ who examined the bone marrow in patients with clinically early malignant disease of various types. In lung cancer cases, cells were found which were regarded as "definitely malignant" or "suspicious" in over 50 per cent of patients who were candidates for radical treatment. Later, Mitchell⁴⁰ showed good correlation between these bone marrow findings and prognosis. The significance of this work in regard to planning treatment and estimating prognosis for the individual case is not entirely clear, although it is now felt⁴⁵ that if malignant cells are definitely present on marrow examination in cases of undifferentiated or oat cell carcinoma of the lung, surgery should be avoided.

Surgery itself can certainly contribute something to the dissemination of lung cancer,⁸ but whether the increase of malignant cells in the blood stream in association with surgery is clinically significant (in bronchogenic carcinoma) is a moot point. It is likely that a potentially lethal tumor migration occurs long before surgical manipulation of the tumor. The surgical specimen frequently shows blood vessel invasion and this fact alone carries a serious prognosis.⁹

THE RELATIONSHIP OF RADICAL THERAPY TO SURVIVAL

Although the object of radical therapy is "cure," the measure of success is survival.¹⁰ Prolonged survival does not depend necessarily on successful tumor ablation, and, conversely, successful tumor ablation guar-

antees neither cure nor prolonged survival. The relationship (and perhaps even the relevance) of local radical therapy to survival is not well defined. The association of reasonably good survival rates with groups of cases selected for a particular form of treatment adds little or no illumination. The implication, consciously or unconsciously made, that a direct relationship exists between treatment method and survival rate creates confusion. It must always be remembered, when data in regard to selected groups of cases are reviewed, that the absolute *over-all* 1 year survival rate in lung cancer is no better than 20 per cent¹³ (Fig. 11) and that the corresponding 5 year figure is at best in the region of 5-6 per cent^{4,13,30}

Since local therapy can only concern itself with the control of local (intrathoracic) tumor, the efficacy of such treatment can

only be judged by its local results. If this yardstick is used, the treatment of carcinoma of the lung (by surgery, radiotherapy or combinations of the two) is moderately successful since only a minority of patients die from the effects of the intrathoracic neoplasm. If, however, local therapy is judged (or perhaps misjudged) on survival, the results are manifestly very poor for the obvious reason that no really effective life-prolonging treatment is available for metastatic lung cancer in distant organs and tissues. Undeniably, local therapy is sometimes required to control local symptoms; indeed by its local effects alone such treatment contributes to survival, but whether or not anything more than minimal local therapy is generally necessary (particularly for advanced cases) is open to question.³³ The most important determinant of survival in lung cancer is the pres-

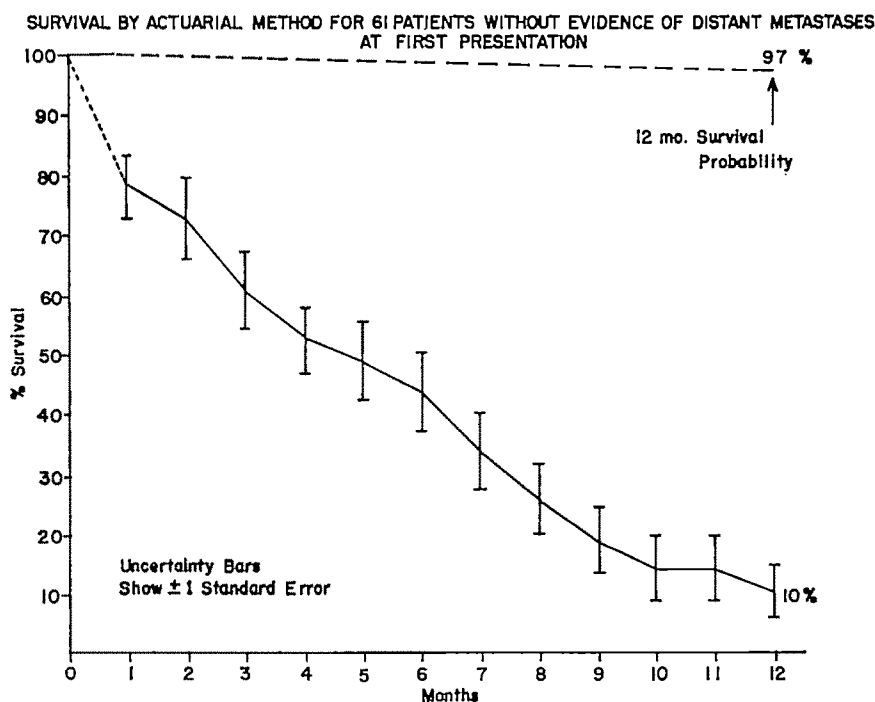


FIG. 11. The survival by actuarial analysis^{5,13,18,19,33} is shown for a total of 61 patients who presented between December, 1961 and June, 1964 at Cincinnati General Hospital. The only patients excluded from this group are those in whom distant metastases were present at the time of diagnosis (17 patients). If they were to be included, the 1 year survival figure would drop to about 7 per cent. It is emphasized that these figures take account of *all* cases seen (including those apparently "early" and amenable to complete surgical resection). Although other reported figures may be somewhat higher, differences are more realistically attributable to biologic factors rather than to therapy.

ence or absence of distant metastases. In more than 75 per cent of patients, the final outcome is determined by metastatic events outside the thorax, even in the presence of persistent chest morbidity due to smouldering activity in the primary tumor, radiation effect, atelectasis, infection, fluid, etc.

It may be concluded that local radiation therapy, even if brought to a pinnacle of perfection and universally applied, could not possibly "cure" more than about 20 per cent of lung cancer patients. In the vast majority of cases, local radical therapy has little or no relevance to survival. If survival figures are reported, and an attempt is made to relate them to a form of treatment, the causes of deaths (*i.e.*, intrathoracic disease versus distant metastases) should be recorded in order to assess the measure of success due to the treatment, and to try to separate this from any apparent success which may be entirely due to the behavior of the disease.

POTENTIALITIES OF CHEMOTHERAPY

The use of nitrogen mustard and related substances for the palliative treatment of bronchogenic carcinoma has been described many times. Roswit (1957)⁶² reviewed the situation and, more recently, Goldman (1963)²¹ assessed results from some of the largest published series. It would be tedious to review this subject again here. It is fair to say in summary that nitrogen mustard is of value in the treatment of superior vena caval obstruction and pleural effusion due to lung cancer, but in other circumstances it has little to offer. Not all lung cancer cases respond to mustard therapy, and response, when it occurs, is generally short-lived according to Hall *et al.*²⁶ and many other writers. Aronovitch *et al.*³ were unable to demonstrate a statistically significant effect on survival or morbidity as a result of an acute course of nitrogen mustard, although they were able to observe significant numbers of regressions in roentgenographic lesions at the expense of considerable drug toxicity. Goldman²¹ obtained good palliation with high dose mustine

therapy, but his series carried a sizable mortality rate and he made no claims for increased survival. Wolf *et al.*,⁶³ by means of a controlled randomized clinical trial, demonstrated that nitrogen mustard alone (compared with placebo) was able to bring about slight prolongation of life, but the advantage of this treatment was discernible statistically only at 1 month post therapy and was no longer evident at 3 months.

Combinations of radiation therapy and acute courses of nitrogen mustard have been disappointing.^{23,28} It has not been possible to demonstrate that nitrogen mustard given around about the same time as irradiation adds anything to survival. There is no evidence to suggest that nitrogen mustard is a chemical radiosensitizer and, whilst its effects may be additive to those of radiation therapy, true synergism has not been demonstrated. Krant *et al.*²⁸ concluded from their study that survival times were independent of the form of treatment and were determined solely by natural selection. Alexander *et al.*¹ found that combination therapy (radiotherapy plus nitrogen mustard, and radiotherapy plus nitrogen mustard plus actinomycin D) actually decreased the median survival time as compared with radiotherapy alone, although they observed good immediate palliation by such combined methods of treatment. Gollin *et al.*^{23,24} have indicated that 5-fluorouracil given as an acute course of treatment together with high dosage localized radiotherapy, although associated with a high toxicity and mortality, can prolong life, at least for some patients. This conclusion is largely dictated by the fact that 4 of 13 patients in their 5-FU plus radiation group survived for over 3 years. The implication from this study is that these 4 long term survivors were either biologically predetermined to be favorable cases, or that an acute course of 5-fluorouracil is capable of dealing effectively with subclinical metastases at distant sites. The former explanation seems more likely, in which case the 5-FU may have succeeded in augmenting

the local effect of radiotherapy. In the series reported herein, when patients who died of the effects of the intrathoracic neoplasm are excluded from the analysis, the results are still in favor of the chlorambucil group (mean survival— $P < .05$, median survival— $P < .025$). This would seem to indicate a real effect on subclinical distant metastatic disease. In studies of this type it is of great importance to record whether or not distant metastases are present at the time of death, particularly in the patients who survive more than 1 year, in order that a better understanding of the mechanism of action of the drug under test can be obtained.

Although nitrogen mustard and other drugs, on the whole, have poor efficiency as cancericidal agents, their ability to attack effectively small tumor foci and circulating malignant cells has been shown experimentally.^{54,55} The value of chemotherapy may be lessened by the fact that it is usually given over a time period which is brief in relation to the over-all period of evolution of the disease.

Karnofsky *et al.*³¹ have emphasized the obvious fact that (lung) cancer must be viewed as a continuous advancing process with an orderly and logical pattern of evolution, and not as an intermittent series of acute crises which either result from exacerbations of symptoms or are created by dramatic forms of treatment. Concepts of the therapy of malignant disease have incorporated little that is consistent with the dynamic nature of the cancer process. Therapy is given, isolated in time, to meet the needs of the moment, but takes little account of the underlying continuum of the neoplastic process. It might appear logical, therefore, to give regular therapy (with an alkylating agent, for instance) to lung cancer patients from the outset (in addition to adequate local radiation therapy) in an effort to suppress or hold in check subclinical metastatic disease. It is suggested that, by this approach, it may be possible to extend the useful life of the patient and delay somewhat the ultimate ap-

pearance of the symptoms that herald the "beginning of the end." The data presented in this paper would suggest that prolonged "suppressive" therapy with carcinostatic agents deserves further investigation.

THE TREND TOWARD PROTRACTION IN CANCER CHEMOTHERAPY

Time-dose factors in cancer chemotherapy have not so far received enough attention, but reports appear from time to time suggesting that time-dose factors indeed have a great deal of relevance to clinical problems. Conclusive data regarding the superiority of one dose regimen over another in humans is difficult to obtain, but some fairly extensive work on the importance of time-dose factors in the control of experimental animal leukemias has been reported by Skipper *et al.*,⁵⁶ Lane,⁵⁴ Goldin *et al.*,⁵³ and others. Sullivan and Watkins⁵⁹ have studied, in patients, variations in toxicity and therapeutic effectiveness of different antimetabolites as related to time-dose factors. This work has been concerned mainly with short term continuous and intermittent administration of drugs by the intravenous or intra-arterial route. Liguori *et al.*³⁶ have studied tissue, serum and urine levels of methotrexate in humans after different dose schedules. Most of this work has been aimed at obtaining optimum conditions for tumor regression, but there has been little scientific work based on the philosophy of tumor suppression.

On a more or less empirical basis, clinical cancer chemotherapy has for many years shown a trend toward protraction. The administration of various hormones in the treatment of breast, prostate, thyroid and certain other neoplasms are practical examples where the concept of maintenance therapy has gained widespread acceptance. In these situations a good response may consist of actual regression of visible, palpable or roentgenologic lesions. Relapse, however, is likely to occur when the hormones are withdrawn and, in any event, such relapse occurs ultimately in spite of continued therapy. It is difficult to be certain

whether or not responses short of actual regression are real, but clinical impressions of subjective improvement and apparent slowing or stasis in the neoplastic process suggest that partial responses do, in fact, occur. It is indeed likely that a whole spectrum of response exists, ranging all the way from complete objective regression to just discernible subjective improvement. The necessity for giving hormone therapy continuously over many months argues for the existence of an underlying "suppressive" mechanism.

In the treatment of acute leukemia, maintenance therapy with an antimetabolite is frequently prescribed after a remission has been induced, in the belief that the remission may, by this means, be sustained for a prolonged period. In the treatment of polycythemia rubra vera and the chronic leukemias, Osgood^{42,43} has used "regularly spaced titrated" treatment with total body radiation or P^{32} in a regimen designed to hold the disease at a subclinical level throughout most of its course. By judicious, regular treatment, relapses can be anticipated and avoided and thereby the need for intermittent dramatic episodes of treatment is minimized.

In regard to "solid" tumors, favorable reports have appeared describing the use of cyclophosphamide as maintenance therapy in the treatment of various neoplasms,²⁷ and in certain children with neuroblastoma.⁶⁰ Intermittent courses of actinomycin D have been used with apparent success for the long time control of Wilms' tumor.²⁹ The use of intermittent intensive courses of therapy or daily maintenance therapy with methotrexate and other drugs in choriocarcinoma in women⁸⁵ has caused much interest. A low dosage maintenance plan for the use of 5-fluorouracil in the treatment of various advanced neoplasms has been described by Cudmore and Groesbeck,¹¹ and the potential value of this type of treatment in lung cancer has been indicated by Helsper and Sharp.²⁸ It has been emphasized that, with these methods, results can often be achieved without extending the treatment

to toxicity.^{11,24,27} Thus, the philosophy of protracted, subtoxic treatment with antineoplastic agents, in keeping with the chronic nature of the cancer process, is gaining some support for the management of leukemias, lymphomas and many "solid" tumors. It may be that the more universal application of these methods can bring about some over-all improvement in the clinical cancer picture, but the degree of benefit achievable will be hard to measure where the natural history of the disease is long.

Bronchogenic carcinoma, because it is a disease of rapid evolution and widespread metastasis, provides a good test system for the concept of suppressive chemotherapy. Denk and Karrer,^{14,15} using prolonged treatment with cyclophosphamide as surgical adjuvant therapy in bronchogenic carcinoma, claimed very marked improvement in survival, although their work is not fully controlled. Similar results have also been reported by other European workers.^{46,47} Ross,^{50,51} who has given maintenance therapy with cyclophosphamide after palliative radiation therapy in a controlled prospective study, has not noted any improvement in survival from this form of treatment. No doubt further trials are justifiable, and the possibilities of combinations of drugs in subtoxic dosages need to be explored.

SUMMARY

"Suppressive" chemotherapy with chlorambucil (as defined at the beginning of this paper) was used in a prospective randomized clinical trial in certain cases of bronchogenic carcinoma. Five hypotheses were originally made regarding the potentialities of suppressive chemotherapy. Data were collected in an effort to test these hypotheses specifically.

The results show that under the conditions of the study, suppressive chemotherapy for bronchogenic carcinoma:

(1) Increased the mean survival time by approximately 80 days ($P = < .025$) and increased the median survival time by ap-

proximately 70 days ($P = <.001$). (Hypothesis 1—substantiated);

(2) Did not affect the quality of survival. General levels of performance ability, symptomatic morbidity, etc., were similar in chlorambucil and placebo (control) patients. (Hypothesis 2—not substantiated);

(3) Did not alter the pattern of the evolution of the disease nor the incidence or type of metastases. (Hypothesis 3—not substantiated);

(4) Seemed to affect survival mainly for patients with undifferentiated and oat cell carcinomas ($P = .0379$). The effect on survival for patients with squamous cell carcinomas is unproven ($P = .162$). (Hypothesis 4—substantiated but further data required);

(5) Was free from risks, side effects and significant clinical toxicity. (Hypothesis 5—substantiated).

The philosophy of the clinical management of bronchogenic carcinoma was discussed in relation to this study. The importance of a realistic assessment of the significance of results was stressed. It is not claimed that chlorambucil has specificity in bronchogenic carcinoma; however, as a representative of the oral alkylating agents, it is simple to administer and dosage is easy to regulate. As used in this study, it appeared to increase the life span of bronchogenic carcinoma patients by a factor of about 1.5 (measured from the time of first therapy).

The validity of the concept of "suppressive" chemotherapy has been substantiated, and it is believed that treatment of this type could be extended and exploited perhaps by using other drugs or combinations of drugs. The implications arising from "suppressive" chemotherapy are discussed.

It is suggested that a trial similar to that described in this article be undertaken by other workers to see if the results are reproducible. It will be important in future trials to commence suppressive chemotherapy earlier (*i.e.*, soon after the diagnosis) and continue it longer than was done in this particular study. It will also be of interest

and importance to specify whether patients in treated and control groups die of local or distant disease.

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RADIOTHERAPEUTIC PROBLEMS BEST HANDLED WITH SPLIT-DOSE THERAPY

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SPLIT-DOSE radiotherapy, in the author's opinion, is capable of significantly improving the 5 year survival rates for patients with radio-amenable malignant neoplasms. The results in the first 50 cases of head and neck cancer treated with split-dose approach have already been published.¹ The results in an additional series of 143 patients with nasopharyngeal malignancy, 21 of whom were treated by split-dose methods with a more than doubling of the 5 year survival rate, will be published soon. Even if one is willing to defer the question of an increase in radiotherapeutic efficiency with this method for several more years, it can safely be said now, after an experience of more than 7 years with more than 1,200 patients, that split-dose therapy certainly does nothing to detract from the results obtained with conventional radiotherapeutic methods.

There remains another facet to the use of split-dose therapy, however, which I consider to be just as important as and perhaps more important than whatever increase in radiobiologic effectiveness may subsequently be shown. This is the greatly reduced radiation morbidity possible with this type of therapy. However creditable the desire of modern radiotherapists to improve results through more intensive therapy, we are left with the inescapable fact that such therapy by its very nature increases radiation morbidity appreciably. Many therapists would answer with the assertion that when a life is at stake, the risk of any correctable and many times non-correctable radiation sequelae is an acceptable one. However, when an alternative method is available, a method that is much gentler and more easily applied, particularly in the aged and infirm, then

familiarity with it will open doors in the problem case which might otherwise remain closed.

The purpose of this paper is to report on certain problem cases encountered in the past several years in which access to the gentler split-dose approach to radiotherapy has meant the difference between an attempt at therapy and rejection of the patient because of the unsuitable risk.

PROBLEM OF THE AGED AND INFIRM

In the past I have had the uncomfortable feeling that high-dose, intensive curative or palliative radiotherapy in the aged and infirm often did more harm than good. Realizing that high-dose therapy was essential if cure or long-term control was to be gained, and lacking the prescience to know which of the poor-risk patients were being taxed beyond their reserves, I have found it a boon, indeed, to be able to fall back on split-dose methods. The rest period of 3 to 4 weeks between halves of a divided-dose series affords an invaluable interval in which to appraise the progress of the patient, stopping treatment if the general condition of the problem case has slipped (which happens remarkably seldom) or continuing the second half of therapy with the patient usually in much better shape after cessation of sepsis, necrosis, tumor shrinkage and so forth brought about by the first half of therapy.

CASE 1. A woman, aged 87 years, had a Grade 4 squamous cell carcinoma, 2.5 cm. in diameter, of the urethral meatus which was found on cystoscopic examination to extend the entire length of the urethra and to involve the entire vesical neck and left lateral wall of the bladder. She had considerable pain but was so weak, frail and infirm that she had to be lifted from the stretcher to the treatment couch.

Radiotherapy data were*: 8[1 month]8 = 5,600 r administered to a single anterior portal 13 by 13 cm. with 6 mev. linear accelerator therapy at a skin-target distance (STD) of 100 cm. Estimated tumor dose (TD) was 5,000 r at 6 cm. at the vesical neck and 5,750 r at 3 cm. at the urethral meatus. The patient completed therapy with few unpleasant sequelae.

Follow-up after 6 months showed a small residual involvement of the anterior vaginal wall. Although she was just beginning to have pain again, she had had 6 months of worthwhile palliation.

This case is presented as a demonstration that intensive high-dose curative radiotherapy can be administered with considerably reduced radiation morbidity even to the very aged and extremely infirm patient.

PROBLEM OF THE VERY YOUNG

At the other extreme of age are the very young in whom the rigors of high-dose radiotherapy can often result in particular unpleasantness when one fails to gain the complete cooperation of the frightened youngster.

CASE II. A girl, aged 7 years, had a right subglottic embryonal rhabdomyosarcoma.

Radiotherapy data were: 10[18 days]15 = 6,450 r TD. A single right lateral 6.5 by 7 cm. portal was treated with Co⁶⁰ at a 50 cm. skin-source distance (SSD) and a dose of 280 r/day.

Follow-up found the patient alive and well with no evidence of residual malignancy 5 years and 1 month after therapy.

This child suffered little or no discomfort during either of her split-dose series, had a mild to moderate sore throat the first 5 to 6 days after completing her initial series, and did not particularly associate the discomfort with her radiotherapy. She proved to be a model of cooperation.

PROBLEM OF POOR RISK DUE TO MEDICAL COMPLICATION

CASE III. A man, aged 74 years, underwent tonsillectomy with removal of a Grade 3

squamous cell carcinoma. Five days later he was subjected to radical dissection of the right side of neck with removal of a metastatic Grade 4 squamous cell carcinoma, measuring 3 by 2.5 by 2.5 cm., from the upper deep jugular region. On the first postoperative day, he sustained a right-sided cerebral infarction with paralysis of the left side of the face, left arm and left leg with complete urinary retention.

Radiotherapy was refused this patient at first because of his extremely grave medical condition. The surgeon, however, urged that treatment be attempted because of the high probability of residual malignancy. It was decided to give at least the first half of a divided-dose course and observe the patient over a 3 week rest interval. He recovered from cerebral infarction during the rest interval and the second series was completed without untoward sequelae. Treatment data were: 11[17 days]13 = 5,048 r TD, 6,390 r being given to a 13 by 15 cm. single portal on the involved side with Co⁶⁰ at an 80 cm. SSD.

Follow-up found the patient alive and well without evidence of residual malignancy 3 years later.

Again, it is quite unlikely that this patient, in an extremely precarious condition from cerebral infarction, would have survived the rigors of conventional radiotherapy pressed to this dose level. In all probability, the therapy would have been terminated short of curative levels.

PROBLEM OF UNDUE DELAY OF RADIO-THERAPY BECAUSE OF MEDICAL COMPLICATIONS

CASE IV. A man, aged 74 years, had an infiltrating transitional cell epithelioma, Grade 4, which penetrated into muscle and involved the left posterior half of the bladder including the left ureteral orifice with extension onto the left lateral wall and vesical neck. There was extravesical induration extending midway to the left lateral pelvic wall.

Radiotherapy data were: 12[2 months]13 = 5,000 r TD or a 200 r TD/day; one anterior and two posterior oblique portals, 11 by 11 cm., were treated in daily succession. It had been planned to start the second series of treatments 3 weeks after completion of the first, but in the rest interval he developed severe urinary sepsis requiring hospitalization in his home community. When he was sufficiently recovered at

* The formula 8[1 month]8 = 5,600 r, used for brevity, signifies that a total of 5,600 r was given in 2 sequences of 8 treatments each, separated by a rest period of 1 month.

the end of 2 months, he returned and completed his second series without further trouble.

Follow-up cystoscopic examination 5 months later showed no evidence of residual neoplasm.

All too often the radiotherapist, when forced to interrupt a planned course of radiotherapy because of life-endangering medical complications, is tempted to abandon any further efforts at radiotherapy, feeling that perhaps the radiobiologic effect of the initial therapy will have been dissipated by the time therapy is resumed. I believe that the tumor-suppressing effect of doses in the region of 2,500 to 3,000 r will persist for 2 to 4 months and often longer, depending on the type of tumor under consideration. These patients should, therefore, not be abandoned as having a hopeless condition; many times, therapy can be restarted and carried to a successful conclusion even after an unplanned interruption of months.

PROBLEM OF IMPENDING NECROSIS

CASE V. A 54 year old man had an infected low-grade epithelioma of the left ala of the nose (illustrated in a previous publication).¹ Conventional continuous radiotherapy was undertaken but midway through it, after an air dose of 2,800 r had been given, the entire bulbous ala turned a necrotic appearing black and it was feared that the entire nose might be sloughed. Treatment was suspended and the patient sent home for 3 weeks. When he returned he had a fairly normal-looking nose and complete disappearance of all visible evidence of malignancy. Therapy was resumed and continued to a total of 4,900 r. The patient remained without evidence of disease 2 years later.

Even more germane than the problem of impending necrosis of cutaneous epitheliomas is the hazard of premature breakdown of a semifluctuant, partially necrotic, metastatic cervical mass. In my experience, once ulceration and subsequent infection of a partially necrotic malignant mass are effected by too vigorous radiotherapy, eradication by any amount of subsequent radiotherapy is next to impossible. Therefore, in the face of too rapid tumor necrosis and impending breakdown and ulceration,

and this is particularly true of large, semi-necrotic, inflammatory, exquisitely tender, pelvic masses with the threat of fistula formation or peritonitis or both, it would seem discrete to suspend therapy midway along and allow suitable time for tumor resolution and consolidation before initiating the second half of therapy. Occasionally, a catastrophic outcome will be thereby avoided.

PROBLEM OF RADIORESISTANT SOFT-TISSUE AND BONE SARCOMA

Usually these lesions are faced with considerable temerity by the radiotherapist, often with a sense of complete futility. Only occasionally is he called on to treat a truly localized bone or soft-tissue sarcoma, obviously because of the established superiority of surgical treatment. Then, faced with the very high probability of blood-borne dissemination which will completely negate his efforts, he must decide between heroic dose levels, which he knows almost assuredly will result in excessive radiation damage, and lesser palliative doses, which he euphemistically calls "pain-relieving" doses and knows will almost certainly fail to control the tumor. Such pessimism, however, regarding the effectiveness of radiotherapy for these localized sarcomas may not be entirely warranted.

Table I shows the results in 76 patients with bone and soft-tissue sarcomas (excluding Ewing's sarcoma, reticulum cell sarcoma and comparable radiosensitive tumors) treated between 1955 and 1960. Groups 1 and 2 comprise 36 patients with known metastatic spread at the time of initial radiotherapy. The results were dismally poor, as might be expected with disseminated disease. Group 3 consists of 19 patients treated with a combination of radiation and radical or resective surgery in which the contribution of radiotherapy was extremely difficult to assess. Group 4, however, consists of 21 patients with localized malignant disease treated intensively, with hope of cure or long-term control. Seven of the 21 (33 per cent) survived for 5 years, a result much more in accord

TABLE I
BONE AND SOFT-TISSUE SARCOMA

	No. of Cases
Group 1, known metastatic spread, <2,000 r	23
Relief of pain for more than 1 year (low-grade chondrosarcoma)	1
No palliation or prolongation of life	22
Group 2, known metastatic spread, 2,000-3,500 r	13
Survival more than 2 years with palliation (1 case of paraspinal leiomyosarcoma, 1 case of abdominal wall synovioma)	2
No palliation	11
Group 3, combined operation and irradiation	19
Five year survival (attributable to operation rather than to irradiation—contribution of radiotherapy [?])	4
Group 4, localized disease, radiotherapy alone	21
Five year survival (1 case of osteogenic sarcoma, 2 of chondrosarcoma, 1 of rhabdomyosarcoma, 1 of liposarcoma, 1 of neurofibrosarcoma, and 1 of synovioma)	7
Split-dose or repetitive therapy	4
Conventional continuous therapy	3
Total	76

with those obtained with the more radio-amenable malignant tumors of the head and neck than with the much more pessimistically regarded radioresistant sarcomas.

Of the 3 patients presented below, the first had a planned split-dose approach, the second an unplanned broken-dose regimen, and the third was treated by the old long-since-discarded intermittent erythema dose technique.

CASE VI. A woman, aged 69 years, underwent partial excision of a Grade 2 fibrosarcoma from the thigh. Extensive tumor tissue was left, however, studding the femoral artery along its entire course from knee to hip.

Radiotherapy data were: 12[6 weeks]12 = 7,200 r administered with Co⁶⁰ affording a tumor dose of 5,750 r at a depth of 4 cm., 300 r per day being given to a single anterior portal covering the anterior aspect of the thigh.

The patient did quite well for 7 years and then returned with a recurrent lesion, 4 by 4 cm., in the anterior part of the right thigh.

Radiotherapy consisted of 2,660 r (air) or 3,225 r (skin) given as orthovolt therapy, 200 r/day being given to a 6 by 6 cm. portal with 250 kilovolt peak (KVP), a 50 cm. STD and a

half-value layer (HVL) of 1.8 mm. Cu. Some superficial necrosis resulted.

The patient was alive without evidence of tumor but with some superficial necrosis 7½ years after start of therapy.

CASE VII. A man, aged 64 years, had a Grade 4 fibroblastic osteogenic sarcoma that produced an 8 by 9 cm. osteolytic defect in the left wing of the ilium. A palliative "pain-relieving" technique of radiotherapy was decided upon. This consisted of 700 r in two increments of 350 r each given to three left pelvic portals: an anterior and a posterior portal each measuring 20 by 20 cm. and a lateral portal measuring 12 by 20 cm., at 250 KVP, a 50 cm. STD, and a HVL of 1.3 mm. Cu. Estimated tumor dose was 1,100 r/6 days.

A palliative "pain-relieving" second series of treatments was given 2½ months later, because there had been some relief of pain. This consisted of 500 r (air) in single increments given to anterior, lateral and posterior pelvic portals, measuring 10 by 15 cm., with the same technical factors as before. The estimated tumor dose was 860 r/3 days.

The patient was seen 2½ months later by a somewhat more aggressive therapist who decided to retreat. This time Co⁶⁰ was administered, 2,400 r being given to opposing anterior

and posterior 14 by 18 cm. pelvic portals, 400 r/day to each portal in rotation. The estimated tumor dose was 2,650 r/12 days.

Two months later Co⁶⁰ therapy was given again, 2,400 r being administered to opposing 12 by 14 cm. anterior and posterior pelvic portals, 200 r/day to two portals, for an estimated tumor dose of 2,550 r/12 days.

Summated dosage data were: $6[2\frac{1}{2} \text{ months}] 3[2\frac{1}{2} \text{ months}] 12[2 \text{ months}] 12 = \text{total TD of } 7,160 \text{ r.}$

The patient was alive and well without apparent activity of the disease 7 years later.

CASE VIII. A girl, aged 9 years, had an osteogenic sarcoma of the upper part of the shaft of the right humerus.

Radiotherapy was given in 1924 with intermediate volt therapy, 135 KVP, a 40 cm. STD and a HVL of 0.3 mm. Cu. Single doses of 700 r (air) were given in single increments to anterior, lateral and posterior portals covering the upper part of the humerus. The first series consisted of an estimated TD of 2,050 r/3 days at an estimated depth of 4 cm. The second series, given 1 month later, consisted of the same dosage, as did also the third series, given 1 month later still. The fourth series, given 2 months later, consisted of 593 r/1 day at a depth of 4 cm., a single dose of 525 r being given to a single anterior humeral portal with 200 KVP, a 50 cm. STD and a HVL of 1.0 mm. Cu.

Summated dosage data were: $3[1 \text{ month}] 3[1 \text{ month}] 3[2 \text{ months}] 1 = \text{total TD of } 6,743 \text{ r.}$

The patient was alive and well 38 years later.

The results in these three radioresistant sarcomas, while not exactly typical of the usual results obtained with radiotherapy, do show that such lesions can in certain instances be eradicated or controlled for long periods with judiciously applied high-dose therapy.

Split-dose therapy is an alternative to the supralethal dosage employed for radioresistant soft-tissue and bone sarcomas. It is my personal conviction that the biologic effectiveness of such therapy is considerably greater than that of therapy by the conventional continuous method and that it affords an excellent means of patient selection. Many an unfortunate patient destined to succumb to blood dissemination

of his malignant disease can be discovered before the completion of such discontinuous therapy and spared the untoward effects of high-dose irradiation.

PROBLEM OF UNCERTAINTY OF MULTICENTRIC SPREAD

Probably one of the most frequent and vexing problems to face the radiotherapist is that of the patient who apparently has a localized primary or solitary metastatic lesion that would ordinarily be treated with high-dose methods yet who has vague unexplained symptoms elsewhere which may or may not be indicative of generalized spread of his disease that would completely negate the effect of intensive local therapy and which cannot be confirmed or excluded with routine diagnostic measures. This is particularly common with carcinoma of the lung, in which the therapist is especially sensitized to the possibility and probability of generalized spread yet cannot demonstrate such spread at the time that he must decide on definitive treatment of the primary lesion. The following patient with proven, apparently unicentric metastatic spread on one side of the pelvis yet with vague ill-defined pain originating on the opposite side is an example.

CASE IX. A man, aged 66 years, had undergone excision of a Grade 3 lipomyxosarcoma three times prior to forequarter amputation of the left arm and shoulder girdle. A year and a half later he presented with severe pain in the left hip and pelvis. Examination revealed an orange-sized metastatic mass lateral to the left lobe of the prostate. Rectal biopsy confirmed the diagnosis of Grade 3 lipomyxosarcoma. Although the right side of the pelvis was clear on examination, the presence of right-sided pain, even though mild, led to some hesitancy in initiating high-dose palliative therapy to the left side of the pelvis. Split-dose therapy, however, afforded a 30 day interval in which the problem of the right-sided pain could be further appraised. At the end of 30 days the pain on the right side had completely disappeared, there was excellent beginning resolution of the metastatic mass on the left side, and it was decided

to proceed with further therapy to the apparently unicentric metastatic mass.

Radiotherapy data were: 11[30 days]16 = 4,865 r TD. Opposing 14 by 15 cm. left pelvic portals were given 340 r/day in rotation with Co^{60} at an 80 cm. SSD, or a daily TD of 180 r.

One year later the patient was symptom-free with no evidence of pelvic neoplasm.

The added time that one is allowed when using split-dose therapy affords an invaluable opportunity for patient selection. In a series of almost 100 bronchogenic carcinoma cases treated with the split-dose method, the 1 year survival rate was neither better nor worse than that obtained with the conventional method. It was my impression that both methods failed not because of inability to control the local problem but because of the high incidence of distant spread. However, a much less important secondary advantage, noted with the bronchogenic carcinomas treated with the split-dose method, is that 16 per cent of patients so treated were spared the second half of their high-dose program, either because of recognizable metastatic lesions that had developed during the rest interval or because a precipitous decline in their general condition presaged a hopeless outcome and the futility of further radiotherapy. I do not anticipate that split-dose methods or any other improvement over conventional methods will significantly improve the survival rates for patients whose malignant disease has a high predilection for distant spread until some means is found for control of the systemic component of the disease. Until then, however, the judicious use of interrupted therapy can eliminate many of the cases with systemic dissemination who could not possibly benefit from completion of local high-dose programs.

PROBLEM OF RADIOVULNERABLE ORGANS
WHERE REDUCTION IN TREATMENT
VOLUME IS HIGHLY DESIRABLE

An additional highly desirable feature of the use of split-dose methods for bronchogenic carcinoma and other pulmonary

malignant tumors is the possibility it affords for reduction in treatment volume at the start of the second half of therapy. The previous publication¹ illustrated 2 such cases of bronchogenic carcinoma and 2 similar cases of Hodgkin's disease in which the size of the tumor had decreased appreciably in the rest interval between halves of a divided-dose series and in which a significant reduction in treatment volume was possible, thus avoiding the inevitable radiation pneumonitis or fibrosis or both, which follow high dosage to large volumes over the lungs. Theoretically, the same advantage should accrue in split-dose treatment of large volumes over the upper part of the abdomen with the ever present danger of radiation nephritis. In actual practice, however, the reduction in tumor size or mass during the rest interval is nowhere nearly as sharply delineated in the upper part of the abdomen on physical examination as it is in the chest seen on roentgen examination. Here, a reduction in treatment volume is a possibility in the great majority of cases.

PROBLEM OF HOPELESS CASE IN WHICH
ANYTHING SHORT OF INTENSIVE
RADIOTHERAPY IS COMPLETELY
FUTILE

Another of the most vexing of radiotherapeutic problems is the apparently localized but probably hopeless internal, particularly gastrointestinal, malignant tumor wherein the patient's general condition does not permit intensive radiotherapy. The following are examples of carcinoma of the esophagus and the stomach, both recurrent after operation, and of primary islet cell carcinoma of the pancreas which many therapists would reject as unsuitable for radiotherapy or, if accepted, they would limit to the moderate or limited-dose range of therapy, which would almost certainly prove inadequate. In each case high-dose curative or palliative therapeutic dose levels were attained with minimal radiation morbidity and significant palliation was afforded.

CASE X. A man, aged 77 years, with carcinoma of the middle third of the esophagus underwent transthoracic resection of the esophagus and a portion of the stomach with end-to-end esophagogastrostomy. The primary lesion, an epithelioma measuring 5 by 3.5 by 3 cm., extended through the muscular wall; one paraesophageal lymph node was found to be metastatically involved.

Six months later a large retrocardiac recurrent lesion was found displacing the transposed stomach anteriorly and there was a malignant mass measuring 5 by 7 by 5 cm. in the surgical incision on the posterior chest wall. Biopsy of the mass disclosed Grade 4 squamous cell epithelioma.

Radiotherapy data were: 14[22 days]12 = 5,000 r TD, 190 r TD/day being given with 6 mev. linear accelerator therapy through two opposing 11 by 29 cm. portals obliqued so as to cover the off-center cutaneous metastatic lesions on the posterior chest wall.

Six months later the cutaneous recurrent lesion on the chest wall had completely regressed but a persistent ulceration was left with continuing drainage. An additional 1,600 r (400×4) was given to the cutaneous ulcer with tangential Co⁶⁰ therapy.

The patient was alive and swallowing well, 1 year later although use of an analgesic (empirin compound with codeine phosphate No. 3) was found necessary to control pain.

CASE XI. A man, aged 37 years, underwent subtotal gastric resection for an extensive Grade 4 adenocarcinoma of the upper two-thirds of the stomach with involvement of the esophagogastric junction and multiple regional lymph nodes. Four months later a gastrointestinal roentgen examination demonstrated an extensive polypoid carcinoma at and below the esophagogastric anastomosis.

Radiotherapy (first series) consisted of a tumor dose of 2,346 r given in 18 days, 2,500 r being given to anterior and posterior 15 by 15 cm. gastric portals with Co⁶⁰ at a 50 cm. SSD.

Four and one-half months later there were recurrent symptoms of obstruction and a repeat gastrointestinal roentgen study revealed some increase in size of the large polypoid carcinoma with a possible gastrocolic fistula.

The second series consisted of an additional tumor dose of 1,794 r/13 days given with the same technique for a total of 4,340 r in 4½ months.

The patient was alive and well 5 years later and roentgenograms of the stomach showed no evidence of residual gastric malignancy.

CASE XII. A man, aged 30 years, underwent abdominal exploration because of recurrent attacks of hypoglycemia. Operation revealed a functioning islet cell carcinoma, Grade 2, a huge multinodular tumor involving the body and head of the pancreas with metastasis to the region of the celiac axis, a 4 cm. metastatic mass in the adjacent right lobe of the liver, and a 10 cm. mass in the left lobe of the liver. Resection was not attempted. At first, radiotherapy was not thought advisable but it was decided finally to try the then highly experimental split-dose method.

Radiotherapy data were: 4[7 days]6[15 days]12 = 3,650 r TD, 300 r/day being given to an anterior or a posterior 15 by 15 cm. portal with Co⁶⁰ at an 80 cm. SSD.

This produced a satisfactory remission of the patient's hypoglycemic attacks which, however, began to recur 2½ years later. Re-exploration revealed the liver to be clear but there was a persistent or recurrent nodular mass involving the head of the pancreas, with a metastatic node adjacent to it in the mesentery of the small bowel.

Retreatment, advised for palliative purposes, was as follows: 4[7 days]5[18 days]12 = 3,700 r TD, 300 r/day being given to an anterior or a posterior 17 by 18 cm. abdominal portal with Co⁶⁰ at an 80 cm. SSD.

The patient was alive 4½ years later (7 years after original radiotherapy) although minor hypoglycemic attacks were again starting which prompted a trial of treatment with prednisone.

Probably no more hopeless problems can be envisioned than these three, yet in each instance high-dose palliative radiotherapy productive of worthwhile palliation was possible by split-dose methods with a minimum of radiation morbidity. It would appear highly likely that any compromise of dosage levels here would not have produced anything like the degree of palliation obtained.

PROBLEM OF LARGE-VOLUME REQUIREMENTS (TOTAL ABDOMINAL THERAPY)

Perhaps one of the most physically taxing of all routine radiotherapeutic pro-

cedures is the treatment of the entire abdomen, particularly common with postoperative carcinoma of the ovaries. Split-dose methods with a rest interval of 3 to 4 weeks between halves of a series can materially lessen the severe radiation toxicity that all too often accompanies such large-volume therapy.

CASE XIII. In a woman aged 50 years, abdominal exploration revealed a Grade 4 adenocarcinoma of one ovary with multiple omental and peritoneal implants. Total abdominal hysterectomy and partial omentectomy were performed with removal of some larger pelvic and omental implants.

Postoperatively, 125 mc of Au¹⁹⁸ was instilled into the abdomen. Ten days later, split-dose Co⁶⁰ therapy to the entire abdomen was initiated. Treatment data were: 14[20 days]14 = 2,900 r TD, two large anterior 14 by 20 cm. portals and two correspondingly opposed posterior abdominal portals being treated, with 300 r to one field per day being given at an 80 cm. SSD.

The patient was living and well 2½ years after therapy except for mild hypertension (160/98 mm. Hg), Grade 1 albuminuria, Grade 1 to 2 pyuria, and microhematuria, which raised the question of possible mild radiation nephritis.

The reduction in radiation morbidity following this and similar split-dose programs has been sufficient to cause me to make this a standard approach in the treatment of carcinoma of the ovary.

PROBLEM OF PREVIOUS HEAVY RADIOTHERAPY

The impracticality and excessive risk of high-dose radiotherapy for recurrence following a previous all-out attempt with curative doses is well established and it is seldom that such a second attempt is ever made by an experienced radiotherapist. Prior to the split-dose era, I had never successfully re-treated a previous heavily irradiated carcinoma of the head or neck or both. The following case illustrates one of the rare exceptions wherein the excessive risk of repeat therapy was avoided by the judicious use of split-dose therapy.

CASE XIV. A man, aged 62 years, underwent total laryngectomy for a Grade 4 squamous cell epithelioma measuring 2 by 1.5 by 1.5 cm. that involved the lower portion of the epiglottis and adjacent aryepiglottic fold.

Postoperative orthovolt therapy was employed, 5,300 r TD/24 days; 3,600 r (air) was given to opposing 7 by 7 cm. right and left lateral cervical portals with 250 KVP at a 50 cm. STD and a HVL of 1.3 mm. Cu.

A recurrent tumor noted in the left side of the neck 4 years later was removed by radical dissection of the left side of the neck. A Grade 3 squamous cell epithelioma, 2.5 cm. in diameter, was removed from the mid deep cervical region. The neoplasm was fixed to the common carotid and some tumor was left after resection.

Figure 1 shows the appearance of this patient's skin when he was again referred for consideration of postoperative radiotherapy.

Radiotherapy data, second series, were: 6[10 days]7[19 days]7 = 3,750 r TD, a single lateral 10 by 12 cm. portal being treated with Co⁶⁰ at an 80 cm. SSD.

The patient remained well without undue radiation sequelae or evidence of recurrent malignancy for another 4½ years, when his death was reported to us. Unfortunately, we do not know whether he died of recurrent malignancy or intercurrent disease.



FIG. 1. Appearance of skin when patient was referred for postoperative radiotherapy.

While it is in no way implied that the use of split-dose radiotherapy will allow successful re-treatment of more than a very occasional patient with recurrent malignancy after prior radiotherapy, it is my conviction that when such is attempted on the rare occasion when the pressures are great, only split-dose methods should be used.

PROBLEM OF UNPROVEN RECURRENCE

Occasionally, a malignant tumor recurs after a previous radical surgical extirpation in such a location and is of such a nature that biopsy confirmation is not possible short of further radical surgical intervention or exhaustive and unrewarding elaborate diagnostic procedures. While "a trial of radiation therapy" sounds like terminology of a bygone era, there is still the occasional case, such as the following, in which the radiotherapist is unwilling to commit the patient to intensive therapy in the face of so much uncertainty. With split-dose methods, however, the therapist can usually determine, after observation of the tumor response or palliative relief afforded by the first half of a divided-dose series, whether additional therapy, that is, the second half, is warranted.

CASE XV. In a woman, aged 34 years, a Grade 2 neurofibrosarcoma of the left sciatic nerve was excised as high as possible in the sciatic notch. Eight months later she returned with pain in the hip and buttock so excruciatingly severe that there seemed no question of malignant recurrence. Chordotomy was offered but the patient refused.

Radiotherapy, first series, consisted of 3,500 r/10 days given to a 10 by 16 cm. left gluteal portal with Co⁶⁰ at a 50 cm. SSD, an estimated TD of 2,415 r being attained at a depth of 6 cm.

Some 3½ months later the patient returned for re-evaluation. She had had moderate relief of pain in the interim but she still had moderate discomfort. Further treatment with Co⁶⁰ was undertaken, 3,500 r/10 days being repeated to the same portal with Co⁶⁰ at an 80 cm. SSD for an estimated TD of 2,590 r. The total TD was 5,000 r/5 months.

The patient was alive and well 4½ years later.

In combatting cancer, one should not be content with even a good palliative result from moderate-dose therapy if the localization and biologic characteristics of the neoplasm are such that one might conceivably hope for long-term control or even eradication. Rather than wait for the inevitable resurgence of malignant activity with renewed growth and neoplastic aggressiveness before resorting to a second palliative attempt with radiotherapy, it seems much more reasonable, if the tolerance of the patient will permit, to give additional therapy while the neoplasm is still small, quiescent and inactive from the first series. In my experience, the biologic effectiveness of such additional therapy is considerably enhanced and the prospects for long-term control, provided dissemination does not take place, is appreciably improved.

PROBLEM CASES IN WHICH SEVERITY OF TREATMENT REACTIONS ORDINARILY MILITATE AGAINST VIGOROUS THERAPY

Primary carcinoma of the prostate is seldom if ever regarded as amenable to radiotherapy. Not only are few such cases successfully treated and controlled but the severity of treatment reactions in this region is such as to discourage all but the most determined. I have gone through three eras in attempting to treat primary carcinoma of the prostate by irradiation. The first was with orthovolt therapy in the early 1950s when the treatment reactions were completely intolerable. The second was at the beginning of the cobalt era in the mid 1950s when the reactions were somewhat less but still sufficient to discourage our urologists from referring these patients. The third was in the late 1950s and early 1960s when the reduction in radiation morbidity afforded by split-dose methods was enough to allow accumulation of a sufficient number of such cases to attempt a cursory if somewhat premature appraisal of treatment.

Table II shows the results obtained in the

TABLE II
CARCINOMA OF THE PROSTATE

	No. of Cases
Group 1, very extensive regional disease, frozen pelvis in some, local pain in prostate, rectum or perineum	12
Died too soon for evaluation	5
Living (6 had severe pain before treatment)	7
Relief of pain: Complete	4
Minimal	1
None	1
Objective regression: Complete	2
Minimal	4
None	1
Group 2, young men, early lesions (preferred not to jeopardize sexual potency by castration, estrogen therapy or operation)	7
Objective regression: Complete	4
Moderate	2
None (died in less than 1 year)	1
Group 3, miscellaneous	7
Complete regression (castration and Co ⁶⁰ therapy)	2
Control of persistent bleeding	2
Advanced local disease and obstruction	3
Died in hospital	2
Helped	1
Total	26

first 26 patients with primary carcinoma of the prostate treated by split-dose methods who were followed 1 to 4 years. These patients were all treated by essentially the same method: a single perineal portal, usually measuring 8 by 10 cm. or larger, depending on the extent of the tumor, was used with the patient in the lithotomy position and in stirrups. Cobalt 60 therapy at an 80 cm. SSD was employed, 300 r/day being given for 10 days, for a total of 3,000 r; then treatment was suspended for 3 weeks. Except for mild to moderate diarrhea usually lasting 4 to 5 days after this first series, there were few if any radiation sequelae and the patient returned at the end of 3 weeks to complete the second half of therapy given in the same manner in relative comfort. A total of 6,000 r was thus given in slightly more than 40 days, with an estimated tumor dose of approximately 4,500 r at 6 cm.

Group 1 (Table II) is comprised of 12 pa-

tients with extensive regional disease, often with solid infiltration from one lateral pelvic wall to the other. Five patients died of advanced disease too soon for the results of such therapy to be evaluated. Of the remaining 7, six had severe pain prior to treatment; of the 6, four had complete relief, one had minimal relief, and one had no relief, a seemingly worthwhile palliative result from a technique of therapy with a minimum of radiation sequelae.

The much more interesting group, however, is Group 2 consisting of 7 young men with early lesions. These men preferred not to jeopardize their sexual potency by castration, estrogen treatment, or operation, and radiotherapy was undertaken as a decidedly unproven alternative. Of this group, complete regression of all palpable prostatic abnormality was noted in 4, moderate regression in 2, and no regression in 1.

While these results are not going to

change the accepted treatment of primary carcinoma of the prostate, it is well to bear in mind that, faced with renewed activity of a regionally limited prostatic cancer after previous estrogen therapy and castration have started to fail, or with an occasional younger patient who rejects both castration and estrogen therapy, the therapist has an alternative method, that of split-dose radiotherapy, which he can fall back on with a minimum of radiation sequelae.

PROBLEM OF CERVICAL CANCER COMPLICATED BY INADE- QUATE RADIUM THERAPY

In an occasional patient with a malignant tumor of the cervix, it is impossible, either because of previous surgical treatment or because of a bulky occluding intrauterine component of the tumor, to give the usual full complement of intrauterine and intravaginal radium. Occasionally, radium therapy is limited by necrosis, sepsis, urinary complications, fistulas or even a weakened debilitated condition of an elderly patient with cervical carcinoma in whom simple placement of intrauterine applicators is an overly taxing procedure.

CASE XVI. In a woman, aged 74 years, with a Stage IV, Grade 3 squamous cell epithelioma of the cervix or vagina, or both, the entire upper two-thirds of the vagina was occluded by an exophytic malignant growth. The corpus was two times normal size; there was solid nodular infiltration of the right broad ligament and fixation to the right lateral pelvic wall, and there was cystoscopic evidence of involvement of the base of the bladder near the right ureteral orifice.

Only limited radium therapy was possible; 2,100 mg. hr. in 4 vaginal applications was given. Intrauterine use of radium was precluded by the size and location of the tumor.

Split-dose 6 mev. linear accelerator therapy was started concurrently with the radium. Treatment data were: 12[22 days]12=4,912 r TD, anterior and posterior 16 by 16 cm. portals being treated in rotation. I had intended originally to try the intrauterine part of the radium therapy when she returned for her second course after the bulk of the cervical tumor had

shrunk. However, regression had been so complete 3 weeks after the first series that there was no longer any visible malignant growth of the upper cervical canal or portio vaginalis and further uterine radium therapy was deferred.

Nine months after therapy a small umbilical nodule removed surgically proved to be metastatic Grade 4 squamous cell epithelioma.

One year after therapy the patient was well and apparently in good health with no palpable evidence of pelvic malignancy. She did, however, have a mild factitial proctitis.

CASE XVII. A woman, aged 52 years, had recurrent carcinoma of the cervix with frozen pelvis. Ten months after radical hysterectomy and bilateral lymphadenectomy elsewhere, she was found to have recurrent malignancy at the vaginal vault with bilateral infiltration of the broad ligament out to the pelvic wall. Biopsy of the vault confirmed a diagnosis of Grade 3 squamous cell epithelioma. Intravenous pyelograms revealed bilateral hydronephrosis with markedly impaired excretion on the left. The concentration of blood urea was 46 mg./100 ml. Abdominal exploration revealed metastatic tumor invading the anterior abdominal wall, terminal ileum, bladder and pelvic peritoneum bilaterally. An ileal pouch operation and bilateral ureteroileostomy were performed and the patient was referred for a trial of radiotherapy.

Radiotherapy data were: 11[6 weeks]14 = 5,000 r TD, given with 6 mev. linear accelerator therapy at a 100 cm. STD, 275 r being given to opposing anterior and posterior 23 by 18 cm. pelvic portals on alternate days. During the first series, limited radium therapy was given, 1,500 mg. hr. in three applications to the vaginal vault.

One year later the pelvis was completely free of palpable tumor and the patient was apparently well and in good health except for occasional bleeding from factitial proctitis.

Obviously, limited radium therapy severely handicaps the successful management of cervical carcinoma. Unfortunately, the very factors that limit radium therapy are many times also conducive to the curtailment of intensive high-dose external irradiation. Faced with the necessity of compensating for the limited radium contribution, or troubled with a problem case in which there are impending obstructions of

the urinary tract and azotemia, pelvic sepsis, impending breakdown of an inflammatory or seminecrotic pelvic mass or possible fistula formation or both, and many other complications of cervical malignancy, access to split-dose methods can mean the difference between successfully completing the necessary dose requirements and abandoning the patient before completion of therapy because of the excessive risk involved.

PROBLEM OF HEMATOPOIETIC DEPRESSION
OR OTHER COMPLICATIONS OF
CONCURRENT CHEMOTHERAPY

With the ever increasing use of chemotherapy in conjunction with radiotherapy, hematopoietic depression and other complications of chemotherapy are an ever growing problem for the radiotherapist, often necessitating unplanned interruptions in therapy. Until recent years, depression of the leukocyte count to less than 2,000 or 1,500/cu. mm. was checked daily with great care and apprehension. Occasionally, the counts would reflect recovery after only a few days but more often than not a delay of 2 weeks or more occurred before the counts increased enough to make it seem safe to resume therapy. Now, however, these patients are routinely sent home with instructions to return in 3 to 4 weeks to resume therapy.

CASE XVIII. A woman, aged 56 years, had a Grade 3 papillary adenocarcinoma, 15 cm. in diameter, of the left ovary with multiple metastatic implants in the omentum, entire abdominal peritoneum, tubes and right ovary with considerable bloody ascitic fluid.

After a preliminary loading dose of cyclophosphamide (cytoxan; 4 doses of 400 mg. each given intravenously), total abdominal therapy with Co⁶⁰ was started. Treatment data were: 7[3 weeks]20 = 3,100 r midabdominal TD, single large anterior and posterior 22 by 28 cm. portals being treated on alternate days with 150 r/day being given to each field in rotation. Therapy was interrupted on the eighth day of treatment because of a cyclophosphamide-induced leukopenia (leukocyte count 1,400). The patient returned in 3 weeks with essentially normal counts and therapy was resumed and com-

pleted without untoward sequelae. Maintenance treatment with cyclophosphamide was resumed 1 month after completion of radiotherapy and was continued at 50 mg. orally per day.

Two and one-half years later the patient was apparently well and in good health.

With the chemotherapeutic regimens we employ, I have never seen a patient have serious trouble from temporary leukopenia during the rest interval while at home, nor have I seen the leukocyte count fail to reach a satisfactory level by the time of the return visit, 3 to 4 weeks later.

SUMMARY AND CONCLUSION

A series of illustrative radiotherapeutic problem cases, mostly borderline ones, is presented. These were among many in which access to the much less traumatic split-dose approach to irradiation often meant the difference between an attempt at treatment and either rejection of the patient because of the excessive risk involved or lowering of the total dose levels to the point of futility. In addition to the improved therapeutic results that seem possible with this method, the much kinder, more gentle course experienced by the elderly debilitated patient in need of vigorous radiotherapy is indeed a strong argument in favor of this type of therapy. Furthermore, there is the large group of problem cases in which the radiotherapist, lacking the gift of prescience, cannot be entirely sure that his localized high-dose efforts will not produce more harm than good or will be completely negated by the presence of undetected generalized disease. Split-dose methods, with their possibilities for added time and in certain cases for strategic retrenchment, afford an excellent means of patient selection and treatment modification.

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EXPERIENCE WITH HYPERBARIC OXYGENATION IN CLINICAL RADIOTHERAPY*

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THE role of oxygen as a factor in radio-sensitivity of biologic materials is generally accepted. The application of this principle to clinical radiotherapy as suggested by Gray *et al.*⁹ has not yet proved to be a significant factor in the treatment of human malignancy. The earliest clinical trial was instituted by Churchill-Davidson, Sanger and Thomlinson⁴ and preliminary results were reported in 1957. This study is still continuing,⁵ but the data obtained are difficult to interpret in terms of superiority of patients treated in hyperbaric oxygen over those treated under normal atmospheric conditions because of the unconventional fractionation techniques used and the lack of suitable controls (at least in the early phases of the study).

Intense interest has been expressed in the application of hyperbaric oxygen in clinical radiotherapy and a number of institutions now have programs under way to study this problem.^{8,12,15,18} The planned program for such a study at the Columbia-Presbyterian Medical Center has been previously presented.¹⁴ Since variations in technique, oxygen pressure and fractionation exist among the various programs which have been instituted and because of the great interest in this subject, it was felt that a report on what has been accomplished so far would be of help to others who may be embarking on similar programs. Of special interest is the degree of normal tissue reactions, the tolerance of patients to the procedure and complications encountered. It is impossible at this stage to make any speculations concerning cure rates or tumor con-

trol because of the relatively small number of cases in the randomized series and the short period of time which has elapsed since the study began.

METHOD

Because of the danger of oxygen toxicity resulting in convulsions in a high percentage of patients breathing oxygen at 4 atmospheres (absolute) or more,⁷ general anesthesia is required. Consequently, in order to make this a practical procedure at this pressure, modification of the conventional radiation fractionation schedule is necessary. This introduces another variable which must be evaluated. In preparation for this study, a large number of patients with various types of malignancy were treated under normal atmospheric conditions on a once-a-week schedule with radiation doses ranging from 1,600 r in two treatments to 4,000 r in four treatments. The preliminary results of the study have been reported.¹⁰ It was felt that a dose of 3,250 r given in three fractions of 1,250 r, 1,000 r and 1,000 r at weekly intervals produced results comparable to 6,000 r in 6 weeks with conventional fractionation, and complications were not significantly increased.

A preliminary study using hyperbaric oxygen was also carried out for two purposes: (a) to gain familiarity with the technique, and (b) to ascertain the correct dosage level. Eighteen patients with various types of malignancy were treated with dosage levels varying from 2,000 r in 2 weeks to 4,000 r in 4 weeks at weekly inter-

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vals (Table I). Despite theoretic considerations which suggested only a slight increase in normal tissue sensitivity at 4 atmospheres of oxygen, it was found that using the same levels of radiation dosage, *i.e.*, 3,250 r in three treatments, resulted in a much greater degree of radiation damage than could be accepted. It was concluded that the corresponding radiation dose at oxygen pressures of 4 atmospheres (absolute) should be 2,200 r in two treatments

spaced a week apart. This produced a reaction in normal tissue similar to that seen in control patients. The dose reduction factor of 1.4-1.5 is consistent with the results in animal experiments¹⁶ and clinical experience.¹⁸

When the randomized series was begun in October, 1960, it was decided to run an additional control group of patients treated with conventional fractionation, *i.e.*, 5,000-6,000 r in 5-6 weeks with treatments three

TABLE I (a)
PRELIMINARY TRIAL OF PATIENTS IRRADIATED IN 4 ATMOSPHERES OF OXYGEN

Diagnosis	Dose	Field Size	Control of Primary Tumor (mo.)	Complications	Remarks
1. Squamous cell epithelioma, base of tongue, bilateral cervical metastases	2,500 r in 2 treatments	10×10 cm.	15	Myelopathy, alveolar ridge necrosis (mild)	Died of myelopathy at 15 months. Tumor in lymph nodes, only, at autopsy
2. Squamous cell epithelioma, base of tongue, bilateral cervical metastases	3,250 r in 3 treatments	10×12 cm.	9	Alveolar ridge necrosis, edema of hypopharynx and fibrosis	Died at 9 months, probably of airway obstruction. No clinical evidence of tumor
3. Squamous cell epithelioma, base of tongue, bilateral cervical metastases	2,500 r in 2 treatments	10×10 cm.	7	Necrosis of epiglottis	Died of widespread metastases at 7 months. Primary site clear but tumor in cervical lymph nodes at autopsy
4. Squamous cell epithelioma, base of tongue, aryepiglottic fold, epiglottis	2,000 r in 2 treatments	10×10 cm.	42	Alveolar ridge necrosis	Living at 48 months. Radical neck dissection at 14 months and laryngectomy at 20 months
5. Squamous cell epithelioma, right tonsil, palate and oropharynx	3,250 r in 3 treatments	6×8 cm.	3 (partial)	None	Died at 10 months of recurrent disease
6. Squamous cell epithelioma, vallecula	4,000 r in 4 treatments	8×10 cm.	27	Necrosis of epiglottis, fibrosis of pharynx and larynx	Died of hemorrhage from throat at 27 months. Clinically free of tumor
7. Squamous cell epithelioma, with unilateral cervical metastases	3,250 r in 3 treatments	8×10 cm.	11	None	Died of local recurrence at 15 months
8. Recurrent squamous cell epithelioma, floor of mouth, post-surgical	2,200 r in 2 treatments	6 cm. circular	0	None	Died at 2 months with persistent disease
9. Squamous cell epithelioma, mid-esophagus	2,200 r in 2 treatments	6×15 cm.	14 (partial)	None	Died at 7 weeks of metastases. Tumor in primary site at autopsy
10. Squamous cell epithelioma, mid-esophagus	3,000 r in 3 treatments	8×15 cm. anterior 6×15 cm. oblique	34	Myelopathy, necrosis of esophagus, fibrosis of mediastinum	Died of myelopathy at 34 months. No tumor present at autopsy
11. Retinoblastoma, recurrent after irradiation	2,000 r in 2 treatments	3 cm. semi-circle	0	None	Died at 6 months of metastases
12. Retinoblastoma, recurrent after irradiation	1,900 r in 2 treatments	2.5 cm. semi-circle	0	None	Alive at 28 months after enucleation
13. Retinoblastoma, recurrent after irradiation	2,000 r in 2 treatments	3 cm. semi-circle	9 (partial)	None	Alive at 14 months after enucleation
14. Retinoblastoma, recurrent after irradiation	2,000 r in 2 treatments	3 cm. semi-circle	10 (partial)	None	Not all of tumor was irradiated. Patient terminal at 32 months
15. Retinoblastoma, recurrent after irradiation	2,200 r in 2 treatments	2.5×3.75 cm.	5 (partial)	None	Alive at 22 months after enucleation for recurrence
16. Squamous cell epithelioma, cervical stump, Stage III	3,000 r in 3 treatments	15×15 cm.	3 (partial)	Jaundice, ileitis, colitis, intestinal perforation	Died at 3 months of radiation complications. Questionably viable microscopic tumor at autopsy
17. Adenocarcinoma, lung	2,500 r in 2 treatments	10×12 cm.	9	Myelopathy, rib necrosis	Died at 12 months with local recurrence
18. Glioblastoma multiforme, left frontoparietal region	2,611 r in 3 treatments	8×10 cm.	0	None	Died at 4 months of persistent disease

to five times a week. This has resulted in some dilution of the experimental material but it is calculated to give us further information with regard to the efficacy of a reduced fractionation schedule.

All patients have been irradiated with the roentgen-ray beam of a 22.5 mev. betatron. Dosage units are in roentgens which have not been converted to rads.

The chamber used for irradiation is constructed of $\frac{3}{8}$ inch steel, 8 feet long and 29 inches in diameter. It is equipped with circular glass windows at each end, monitoring leads and connections and tracks to accommodate a stretcher. The chamber is lifted on to the treatment table by means of a motor-driven chain hoist. Beam localization is performed by an apparatus especially constructed to provide a locus on the outer wall of the chamber to correspond to the central ray entrance point on the skin of the patient inside the chamber for a direct vertical or horizontal beam. More recently, a transparent chamber similar to the one described by Emery *et al.*⁸ has been acquired.

For various technical reasons, as well as to facilitate observation and evaluation, patients were selected for the randomized controlled series who had advanced malignancy of the head and neck or upper thor-

acic region. Since the method is experimental, patients who had a reasonable chance of control by more conventional treatment were not chosen. Only patients with tumors beyond the organ or site of origin by direct extension or lymph node involvement were considered. Because of limitations imposed by the chamber, all the regional lymph nodes were not always treated and radical neck dissection, when indicated, was carried out at a later date.

Certain difficulties are encountered in making a final evaluation. The survival rate can be expected to be poor because of the unfavorable cases selected for inclusion in this study. Ability to control the primary tumor area was considered the only valid criterion of success but clinically this is not always readily ascertained. The problems encountered in carrying out a controlled clinical evaluation of a treatment method have been summarized by van den Brenk.¹⁷

PROCEDURE

A careful evaluation of each patient is made prior to instituting radiotherapy. Direct examination, laryngograms, barium studies, etc. are made to define the extent of tumor and the general medical status is determined. Hospitalization from one day prior to the day following treatment in the hyperbaric chamber is required. Control patients are generally treated as outpatients.

Treatment in the chamber has been carried out in the afternoon. Patients have only liquids for breakfast and then are allowed nothing by mouth. Premedication is seconal, demerol and atropine, administered on call from the anesthesiologist. The patient is then brought to the preparation room adjacent to the radiation facility and placed on the special stretcher. Intravenous anesthesia, pentobarbital, demerol and thorazine, are used to put the patient to sleep. Intubation is accomplished and various monitoring leads are applied. An otolaryngologist performs bilateral myringotomies, since the anesthetized patient is

TABLE I(b)

SUMMARY OF 18 PATIENTS TREATED TO
VARIOUS DOSES OF RADIATION UNDER 4
ATMOSPHERES OF OXYGEN

Tumor Control	
8/18 complete for 2 months or more	
6/18 partial 1½-10 months	
Severe complications	8/18
Death due to complications	5
Longest survival	48 months
Complications:	
osteonecrosis	4
myelopathy	3
necrosis of epiglottis	2
fibrosis	3
intestinal perforation	1

unable to equalize pressure under the rapidly changing conditions in the chamber.

The stretcher is wheeled into the treatment room. The upper portion is released from the wheeled frame and slides along the tracks within the chamber until the point on the skin which coincides with the central ray of the treatment beam is just at the entrance of the chamber. Measurements are made of the coordinates of the point where the central ray enters and of the distance from this point to the outer surface of the chamber. The stretcher is then pushed all the way in until it reaches a stop. The treatment table is positioned before the betatron so that the central ray corresponds to the coordinates previously determined on the outer surface of the chamber. Localization roentgenograms are taken through both thicknesses of the chamber with the betatron beam and are adequate to distinguish the air-containing structures as well as to visualize the bone faintly.

The door of the chamber is closed and the air inside is flushed out by rapidly flowing oxygen. When the oxygen content within is 96 to 98 per cent, the exit valve is closed and pressure built up to 45 lb. per square inch as indicated on the gauge. This is done over a 10 to 15 minute period. Another 15 minutes are allowed to elapse at full pressure before treatment in order to attain oxygen equilibrium in tumor and normal tissues. Irradiation at 1 meter treatment distance requires approximately 30 minutes, after which a rapid decompression in about 10 minutes is accomplished. The patient is then brought to the recovery room and usually sleeps until the following morning.

Monitoring of various physiologic functions is carried out during the time the patient is in the chamber. The electrocardiogram is most important. A microphone attached to the endotracheal tube is helpful as a warning of impending distress or of light anesthesia. A plethysmographic recording of blood pressure had been used at first but has since been abandoned. Other monitoring devices are: a rectal thermo-

couple, closed circuit television viewing and an oxygen polarograph.

RESULTS

At this time it is not possible to provide information concerning survival rates or ability to control the tumor. However, it is possible to present some of the immediate results in terms of patient tolerance, and early and late complications.

The tolerance of the patients to the procedure has been excellent. The main danger is respiratory depression secondary to the overuse of anesthesia. In only 1 patient was this a serious problem. Respirations stopped and a pulse was unobtainable but was restored by external cardiac massage and "lorfan." The patient never became cyanotic. Radiotherapy was then given under full pressure. Minor electrocardiographic changes were noted afterwards during a period of observation, but the patient was not symptomatic in relation to this episode. On two or three other occasions decompression for administration of more anesthesia was required due to the patient's awakening and moving while in the chamber.

Few physiologic disturbances have been noted during compression and irradiation. Respiratory changes are slight and the rate usually remains constant while there is a slight rise in tidal volume. The heart rate slows during pressurization, and this appears to be a vagal effect, since atropinization will abolish or markedly reduce it.

The electrocardiogram shows characteristic changes which become manifest at 10 to 15 lb. pressure, persist throughout pressurization and for a variable period after decompression. The change consists of a doubling of the height of the T-wave, and was observed in nearly all patients whether or not atropine had been previously administered. There is nothing to suggest that the change is of clinical significance.

The blood pressure usually falls slightly during the period of treatment but not to a greater extent than one would expect in patients so anesthetized.

The rectal temperature usually falls dur-

ing treatment and may continue to fall for a short time afterwards, reaching the lowest point of 1 to 2 degrees Fahrenheit below normal about 2 hours after the start of treatment. There is then a rise in temperature to levels of 2 to 4 degrees above normal, the peak usually attained at about 8 hours. The temperature returns to normal over a 24 hour period. It is possible that the initial fall in temperature may be due to the anesthetic drugs used, some of which have a vasodilator action, but it may also be associated with the changes in barometric pressure. The later rise in temperature perhaps may be one of the results of irradiation. The temperature changes are tolerated by the patients without ill effects.

Skin reactions have been minimal except in 2 patients. In 1 patient treated with 3,000 r in three treatments through opposing 15×15 cm. fields to the pelvis, the skin reaction was unusually brisk and reached a moist desquamative stage after a calculated maximum skin dose of approximately 1,800 r (Fig. 1). In a patient with carcinoma of the mid-esophagus, the exit areas of the anterior and each posterior oblique portal attained a marked dry desquamation after a calculated skin dose of approximately 650 r each in single treatments. All other patients demonstrated only a mild tanning at most. The maximum skin dose occurred when 1 cm. of lucite bolus was used because of lymph node involvement and was ap-

proximately 1,500 r when 2,200 r was given to the tumor.

Mucosal reactions were severe and required hospitalization in 1 instance. Beginning mucositis was first noted about 2 weeks after the initial treatment and proceeded to a confluent membranous reaction in a matter of 3 to 5 days. The reaction usually subsided in a month. The reactions were equivalent in severity to those observed with conventional radiation therapy after a dose in the range of 6,000 r in 6 weeks of daily treatment, or 3,250 r in three treatments spaced a week apart under normal atmospheric conditions.

The late complications were seen most commonly in the early group treated to higher doses and have been largely eliminated since the dose was reduced to 2,200 r in two treatment sessions. Edema of the submental region was frequently noted in patients who had had enlarged cervical lymph nodes prior to therapy probably because of interruption of normal drainage pathways. Laryngeal and pharyngeal edema of a marked degree was noted in 2 patients, 1 of whom received 3,250 r in three treatments for a large base of tongue lesion, and the other, 4,000 r in four treatments, for a vallecular tumor. Both patients had permanent tracheostomies. The patient with the base of tongue lesion required a tube for feeding purposes since his swallowing function was severely compromised by pharyngeal fibrosis, and he died at home presumably as a result of complications 9 months after completion of treatment without clinical evidence of tumor. The patient with the vallecular lesion died of hemorrhage probably secondary to radiation damage in the hypopharynx at 27 months, also without clinical evidence of tumor.

One of the most serious late complications encountered was radiation myelopathy. This was seen in 3 patients and might have developed in others had they survived the malignant disease for a longer time. Death was directly attributable to this complication in 2 patients. In one pa-



FIG. 1. Moist desquamative reaction following calculated 1,800 r skin dose in 3 treatments under hyperbaric oxygen in patient with carcinoma of the cervix (146-64-94).

tient with carcinoma of the esophagus, in whom a single anterior and two posterior oblique portals were used to avoid over-irradiating the spinal cord, the patient developed symptoms 29 months after therapy and died at 34 months without evidence of persistent tumor. Myelopathy was confirmed at autopsy. The cord was directly irradiated only through the anterior field and probably received approximately 800 r in a single treatment.

The second patient who died had a very large carcinoma of the base of the tongue with bilateral cervical lymph node metastases. He developed symptoms of myelopathy 8 months after treatment and progressed rapidly to death at 15 months. Autopsy revealed the primary site to be free of tumor but with metastatic carcinoma in cervical lymph nodes and severe degenerative changes in the cervical spinal cord. The dose to the cord had been 2,500 r in two fractions through opposing 10×10 cm. lateral ports which extended posteriorly to include the cervical metastases as well as the primary site.

The third patient who developed radiation myelopathy had the same dose as the second patient but directed to a carcinoma of the left upper lobe and included the upper thoracic spinal cord. About 8 months later, symptoms of myelopathy were noted accompanied by biopsy-proven recurrence involving the upper third of the esophagus. The patient died at 12 months and no autopsy was obtained. However, a myelogram revealed no abnormalities and was consistent, therefore, with radiation myelitis.

It is difficult to ascribe the development of damage to the spinal cord entirely to the oxygen effect. We have noted the late occurrence of myelopathy in other patients treated with massive single doses of radiation under normal atmospheric conditions.² However, studies of oxygen tensions in mammalian and human brains,^{1,6} indicate that some cells in the central nervous system normally exist under low partial pres-

ures of oxygen. Increasing the oxygen available to these cells may markedly enhance radiosensitivity. We have learned since to avoid the spinal cord in all cases. This makes adequate treatment of patients with cervical metastases rather difficult. In some instances it has necessitated omitting treatment of some lymph nodes when the primary site is under treatment, leaving the metastases to be treated separately. This is one reason why we have relied on radical neck dissection to control cervical metastases when indicated.

Osteonecrosis of varying degrees of severity was noted in a number of patients in the early series. Since reducing the dose, it has been rarely encountered or has been of a minor degree of severity. Of 8 patients with head and neck malignancy in the early group, 3 developed alveolar-ridge necrosis, 2 had necrosis of the epiglottis and only 3 had no such complication and survived 2 months, 10 months, and 15 months, respectively, before succumbing to recurrent or persistent cancer. Roentgenographic evidence of rib necrosis secondary to radiation was noted on chest roentgenograms of the patient who was treated for carcinoma of the lung.

Mild alveolar-ridge necrosis has been observed, so far, in only 2 of the 8 patients who had this region in the field of treatment in the randomized series treated under 4 atmospheres of oxygen. Two of 8 patients in the three-treatment control group also developed mild to moderate necrosis which subsequently healed. One of these developed necrosis following radical surgery for recurrence so that it cannot be attributed entirely to irradiation. There are theoretic reasons for believing that radiotherapy under increased oxygen tension will cause an increased incidence of bone necrosis.^{3,11}

Two patients had gastrointestinal tract complications. One with carcinoma of the cervical stump had had a previous subtotal hysterectomy. It is possible that adhesions binding down bowel in the pelvis con-

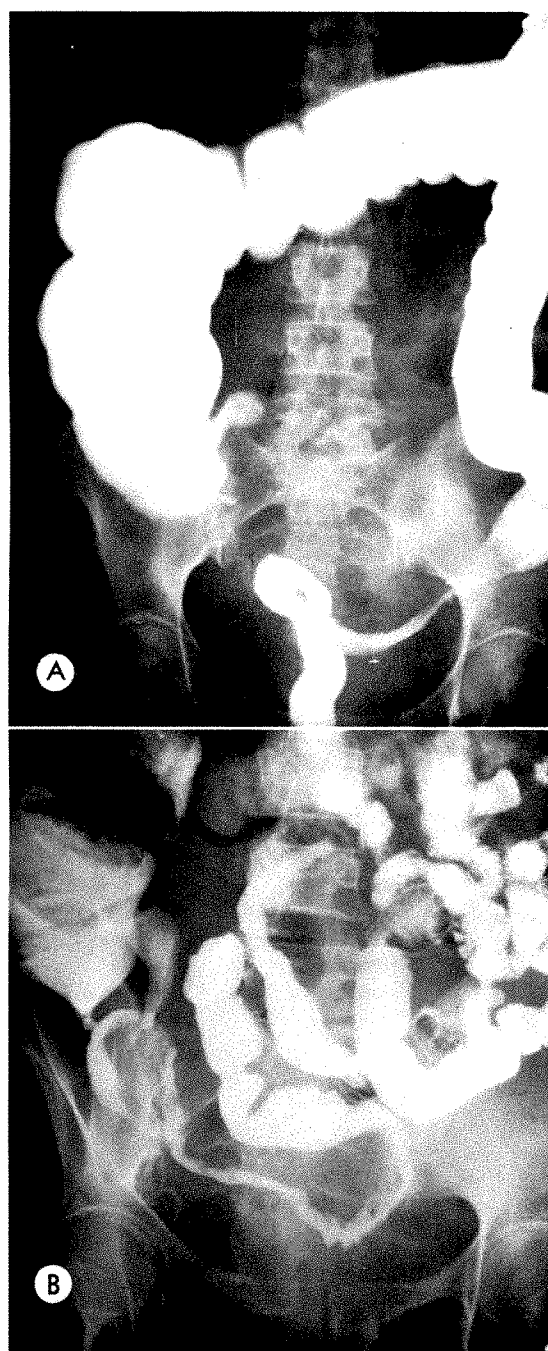


FIG. 2. Same patient as in Figure 1. (A) Marked narrowing of sigmoid colon 6 weeks following 3,000 r in 3 treatments under hyperbaric oxygen to the pelvis for carcinoma of the cervix. (B) Marked narrowing of distal ileum. This segment of bowel was probably bound down in the pelvis following previous surgery.

tributed to the damage. She received 3,000 r in three treatments through opposing 15×15 cm. anteroposterior fields to the pelvis. Severe jaundice and a semicomatose state of unknown etiology developed along with severe enteritis shortly after the third and last treatment. This gradually cleared but the patient expired of intestinal perforation in the region of the appendix after 3 months. Roentgenographic examination revealed severe radiation changes in both the large and small bowel (Fig. 2, A and B). These changes were confirmed at autopsy where greatly thickened intestinal walls and narrowed lumens were found (Fig. 3). Only microscopic tumor of questionable viability was disclosed by the autopsy (Fig. 4).

Moderate radiation effect on the esophagus developed in the patient (Case 11) who received 3,000 r in three treatments for a large carcinoma of the mid-esophagus. This was noted about 4 months after completion of therapy. The patient also developed moderate mediastinal fibrosis. An anterior mediastinal colon transplant was carried



FIG. 3. Same patient as in Figure 1. Autopsy specimen. The rectosigmoid has been split open and separated from the vagina. Black arrow points to necrotic tissue at apex of vagina. White arrow points to thickened bowel wall.

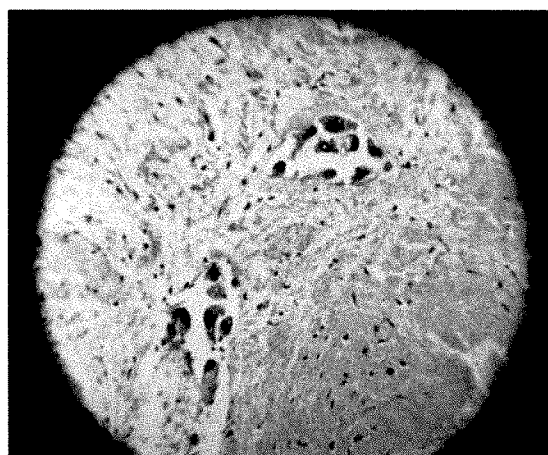


FIG. 4. Same patient as in Figure 1. Microscopic section of tissue from the vaginal apex reveals a few questionable viable malignant cells following radiation therapy.

out but the patient expired at 34 months secondary to the myelopathy described above.

REPORT OF CASES

CASE I, 147-05-48. A 57 year old man had an 8 to 9 month history of sore throat, dysphagia and blood-streaked sputum. A proliferative mass, 2 cm. in diameter, was seen with difficulty on the right side of the vallecula and an additional mass was noted on the left aryepiglottic fold. Biopsy was reported as epidermoid carcinoma. A 1.5 cm. right cervical lymph node was palpated as well as a 2 cm. left cervical lymph node, both at the level of the angle of the mandible.

Radiotherapy was administered through lateral opposing 10×10 cm. portals on April 26, 1960 and May 3, 1960. Each treatment consisted of 1,000 r tumor dose given while the patient was breathing 100 per cent oxygen at 4 atmospheres (absolute). A planned total of 4,000 r in four treatments was not given because of the appearance of severe membranous mucositis on the seventh day after the second treatment.

Following radiotherapy the lymph nodes

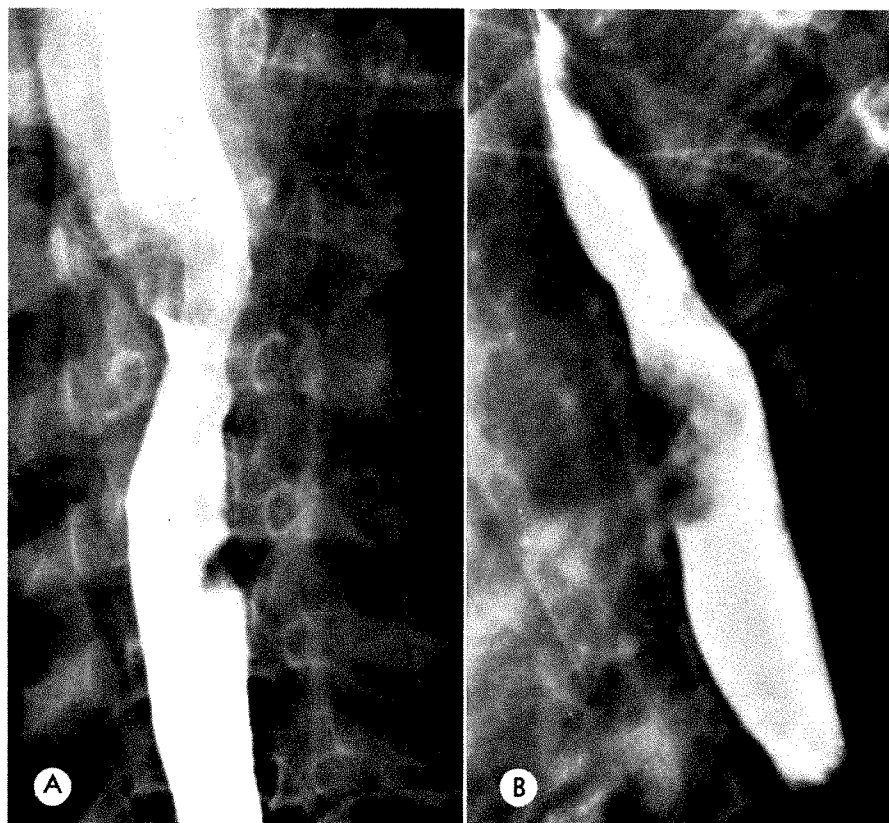


FIG. 5. Case II. A 42 year old female, with infiltrating and polypoid carcinoma involving a 7 cm. segment of esophagus at the junction of the upper and middle thirds. (A) Frontal view. (B) Lateral view.

regressed, the mucositis cleared in 2 weeks and the tumor disappeared. Laryngoscopy and biopsy 5 weeks following completion of therapy revealed no evidence of tumor. Osteonecrosis of the left lower alveolar ridge developed 7 weeks after treatment, presumably about the retained roots of a previously extracted tooth. Necrosis of the mandible has persisted chronically with occasional removal of sequestra, but the degree has lessened markedly in the past 2 years. Post-therapy laryngography revealed a return to normal as compared to the pre-radiotherapy study.

A left cervical lymph node began to enlarge about 11 months after completion of treatment. This lymph node, at the lower edge of the therapy field, was excised in a radical neck dissection on June 9, 1961. Tumor was found invading fat and connective tissue at this site only, and 20 other removed lymph nodes were free of tumor.

Two and one-half years after radiotherapy, swelling of the left false cord and arytenoid was noted on follow-up examination. Biopsy was interpreted as squamous cell epithelioma. No tumor could be found in a specimen obtained from the base of the tongue. A total laryngectomy was performed on January 16, 1963. An ulcerated lesion on the left aryepiglottic fold was demonstrated which proved to be squamous carcinoma. The wound then healed without difficulty and the patient has remained well since, with no evidence of tumor 48 months after treatment for the original lesion.

CASE II, 98-45-40. This 42 year old woman with a past history of excessive alcohol intake developed chest pain and difficulty in swallowing. Roentgenograms showed an extensive polypoid carcinoma of the mid-third of the esophagus (Fig. 5, *A* and *B*) proved by biopsy to be an epidermoid carcinoma.

Radiotherapy consisted of three treatments of 1,000 r tumor dose each on May 10, May 17, and May 24, 1960. Therapy was administered through an anterior 8×15 cm. and two posterior oblique 6×15 cm. portals while the patient was in an atmosphere of 100 per cent oxygen at 45 lb. gauge pressure (4 atmospheres absolute). Following treatment the patient experienced severe radiation esophagitis and a moderate skin reaction at the exit region of the three treatment fields. Two months later an esophagram showed disappearance of all gross tumor and a smoothly constricted mid-esophagus (Fig. 6).

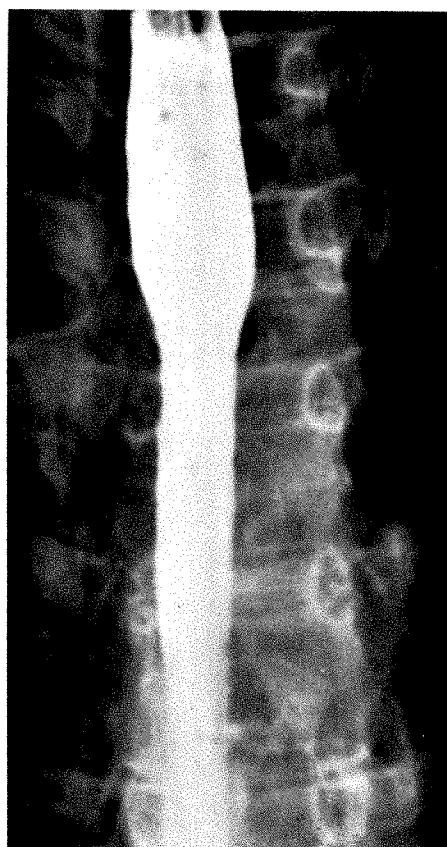


FIG. 6. Case II. Four months after 3,000 r in three treatments under 4 atmospheres (absolute) of 100 per cent oxygen. The esophagus shows mild narrowing without evidence of residual neoplasm.

Dysphagia persisted, and esophagoscopy and roentgen examination 5 months later revealed irregularity of the mucosa and stricture of the esophagus in the treatment field (Fig. 7) and mediastinal fibrosis (Fig. 8). Biopsies of the esophagus and scalene lymph nodes failed to reveal evidence of tumor and this probably represented radiation necrosis. Subsequently, on December 22, 1960, a right colon transplant was performed substernally and the esophagus was bypassed.

The patient recovered without difficulty from the operation and proceeded to gain weight. On October 6, 1961, a resection of a small, superficial squamous cell epithelioma of the anterior floor of the mouth was performed. One year later, 29 months post therapy, the first symptoms of radiation myelopathy were noted. These were difficulty in walking, numbness and decreased temperature sensation in the lower extremities. A diagnosis of transverse myelitis secondary to radiation at the level of T6-T8



FIG. 7. Case II. Six months post therapy the esophageal contour is moderately irregular although biopsy failed to reveal evidence of tumor.

was made. The patient progressively deteriorated and expired on April 3, 1963, over 34 months from the completion of radiotherapy. At autopsy no evidence of tumor could be found and the diagnosis of radiation myelopathy was confirmed.

CASE III, 147-84-52. A 67 year old man noted a painless, slowly enlarging lump in the left side of his neck for several months. Examination revealed a large ulcerative lesion of the left tonsil involving both pillars and the adjacent lateral pharyngeal wall and a 3×5 cm. lymph node in the middle of the left cervical chain. Biopsy of the primary lesion was interpreted as squamous cell epithelioma. Radiotherapy consisted of 2,200 r to the tumor divided in two equal doses spaced 1 week apart through opposing lateral 8×10 cm. portals in 100 per cent oxygen at 45 lb. gauge pressure (4 atmospheres absolute). The tumor responded well to irradiation and disappeared in 1 to 2 weeks. The

lymph node regressed somewhat but did not disappear.

A left radical neck dissection was performed 6 weeks following radiotherapy. Of 51 lymph nodes removed, none showed evidence of carcinomatous involvement. Four months later a small area of radionecrosis developed on the left lower alveolar ridge which healed in 2 months on conservative therapy. The patient was well without complications when last seen 30 months after radiotherapy.

DISCUSSION

The treatment of patients under conditions of increased oxygen tension appeared to be a formidable task when this problem was first approached. However, after the initial difficulties of a new procedure were ironed out, it was discovered that a team consisting of anesthesiologist, radiologist, physicist, and nurse-technician could function very smoothly and the operation took on the aspect of a routine procedure. The minimum time for one treatment, including anesthesia and positioning has been 1½ hours. Since the betatron output is low, this

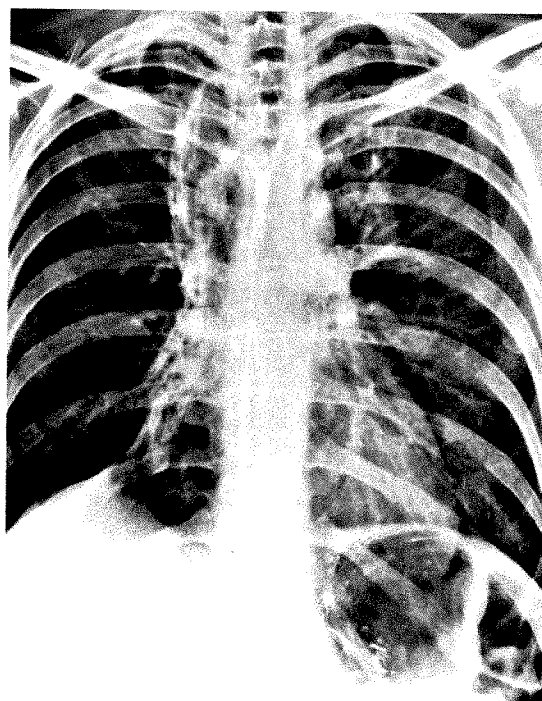


FIG. 8. Case II. Chest roentgenogram 6 months after therapy shows moderate mediastinal fibrosis.

time could be reduced by using a high output linear accelerator.

The procedure is well tolerated by patients. No ill effects due to the procedure itself were noted and only radiation complications such as enteritis in one instance and mucositis in another prevented us from completing the planned course. It is our impression that a course of irradiation consisting of only two or three treatments with short hospitalization is easier on patients than a 6 week course of daily conventional radiotherapy.

Contrary to our expectation, the radiosensitivity of normal tissues was increased during exposure to hyperbaric oxygen. This has necessitated the application of a much lower dose (2,200 r in two fractions spaced a week apart) than we had originally considered. Since we felt that this dose level would be inadequate without the potentiating effect of high pressure oxygen, ethical and moral considerations led us to adopt a higher dose schedule (3,250 r given in three fractions of 1,250 r, 1,000 r, and 1,000 r at weekly intervals). Although this does not conform to the ideal characteristics of a control group, we think it still permits a valid standard for comparative purposes. The same type of complications and problems with dosage were encountered by Madigan¹³ in the Australian study.

Two possibilities are suggested to explain this finding. Either the curve for radiosensitivity *versus* partial pressure of oxygen is incorrect or normal tissues, in part, exist under conditions of low partial pressure of oxygen. The latter explanation seems more likely based on experimental evidence.^{1,3,6}

By regulating our dosage schedule, we have so far avoided most of the problems encountered in the first group of patients treated. The complication rate is now acceptable and apparently no greater than with conventional forms of therapy. Our longest surviving patient (Case 1) is now alive more than 48 months since completion of treatment. He received 2,000 r in two treatments for a squamous cell epithelioma

of the base of tongue, vallecula and aryepiglottic fold with a cervical metastasis. The planned course of 4,000 r was not completed due to severe membranous mucositis. He has had a radical neck dissection and, 19 months after treatment, a laryngectomy for either recurrence or a new primary of the false cord at the lower edge of the radiation field. He has had moderate difficulty with osteonecrosis of the mandible at the site of a retained root, but otherwise has had no untoward complications.

We have been impressed by rapid resolution of intraoral tumors in most cases as well as the rapid response of some greatly enlarged lymph nodes involved with metastasis. In some instances a very definite improvement was noted at the time of the second treatment, only 1 week after the first radiation dose. Tables II, III, and IV list the patients treated in our new series, the tumor control rate and complications. It is too early in the course of this study to make any significant comparisons.

Many factors must be taken into consideration in this study. Whether 4 atmospheres are significantly superior to 3 atmospheres of oxygen is not known. Reduction of the oxygen pressure and utilization

TABLE II
IRRADIATION UNDER 4 ATMOSPHERES OF OXYGEN

Patient	Tumor Control (mo.)	Survival (mo.)	Complications
1	0	2½	—
2	4	12	—
3	17	17	Osteonecrosis (mild)
4	2	8	—
5	0	5	—
6	19	19*	Mucositis, osteonecrosis (mild)
7	0	6	—
8	4	4	—
9	0	2	—
10	4	4	—
11	0	6*	—

* Still alive at time of report.

Tumor control 6/11 for 2 months or more.

Complications 2/11 (none severe).

TABLE III
ONCE-A-WEEK IRRADIATION, NO ADDED OXYGEN

Patient	Tumor Control (mo.)	Survival (mo.)	Complications
1	6	6	Soft tissue necrosis
2	7 (Partial)	7*	—
3	6	6	Edema, fistula
4	10	10	—
5	11	11	—
6	0	9	—
7	3½	31*	Osteonecrosis
8	2½	9	Mucositis
9	23	23*	Osteonecrosis
10	0	2½	—

* Still alive at time of report.

Tumor control 7/10 complete 2 months or more; 1/10 partial. Complications 5/10.

of a transparent chamber would allow treatment in most cases without the need for anesthesia. This would also enable a more conventional schedule to be used and make comparisons more reliable. Such a scheme is now being used for the treatment of glioblastoma patients. Oxygen pressure, the influence of anesthesia, the fractiona-

tion schedule and case selection must be evaluated.

To assess accurately the role which hyperbaric oxygen will play in clinical radiotherapy, many more patients must be treated with this method, adequate controls are necessary and much time must still elapse. It is hoped that the pooled experience of a number of institutions will help in making an accurate assessment of the role of hyperbaric oxygenation in clinical radiotherapy.

SUMMARY

A study of the effects of radiotherapy of human malignancy under conditions of high pressure oxygen has been outlined. Early experience revealed a high incidence of complications because of increased radiosensitivity of normal tissues under these conditions. Subsequent experience has been more favorable and the study is continuing. Some of the difficulties to be expected are presented.

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TABLE IV
IRRADIATION WITH CONVENTIONAL FRACTIONATION IN AIR

Patient	Tumor Control (mo.)	Survival (mo.)	Complications
1	31	31*	Laryngeal edema, hearing loss
2	5	5*	—
3	0	8*	—
4	0	4	—
5	0	10	—
6	0	5	—
7	4½	4	—
8	0	8	Osteonecrosis
9	1½	5½	—
10	0	3	—
11	0	3	—
12	0	7	—

* Still alive at time of report.

Tumor control 3/12 for 2 months or more. Complications 2/12.

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THE THERAPY OF UNBIOPSIED BRAIN TUMORS*

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IN THE case of a suspected brain tumor, the usual practice at the University of California School of Medicine is to obtain histologic verification before institution of therapy. Exceptions, however, are made. In the present report the reasons for such exceptions, the results of radiation therapy in these cases, and the ultimate histologic diagnoses whenever available are discussed.

For this purpose the records of all patients with a suspected brain tumor irradiated between 1934 and 1959, without biopsy, were studied. In this group were 61 patients with definite clinical evidence of a brain tumor, confirmed in most cases by pneumography or angiography. Treated without biopsy, but discarded from the series, were 7 patients in whom the evidence of a brain tumor had been minimal. Four others in whom angiographic evidence had indicated that the tumor was a hemangioma and several patients with metastatic cancer were also discarded. All patients included in the study had been examined by the neurosurgical staff and then referred for radiation therapy. Several had undergone a shunt of the cerebral spinal fluid system and others had had an exploratory craniotomy.

In 38 patients, the reason for referral without biopsy was the location of the lesion, which made surgical procedure unduly hazardous. Lesions were considered too vascular for primary operation in 3 patients and 18 lesions were treated because of the presumptive diagnosis of medulloblastoma.³ In the other 2 patients, posterior fossa lesions had been demonstrated by pneumography but were not seen at exploratory craniotomy.

The 61 patients selected for study were separated into 3 groups. Group I consists of those with lesions in the pons, medulla oblongata, or brain stem. The lesions of Group II were in the mesencephalon, the pineal area, or in the walls of the third ventricle. Lesions involving the cerebellum and roof of the fourth ventricle comprise Group III.

Detailed data regarding age and sex incidence, symptoms, neurologic signs, roentgen findings, and cerebrospinal fluid alterations in similar cases have been described previously and will not be repeated.^{1,2,4,5}

RESULTS

GROUP I. LESIONS OF THE PONS, THE MEDULLA, AND THE BRAIN STEM

This group consists of 21 patients (Table I) with clinical evidence of a tumor in one of the aforementioned sites. Pneumography

TABLE I
GROUP I. PONS, MEDULLA, AND BRAIN STEM
COMPOSITION OF SERIES

No. of Patients	21
Less than 20 years of age	18
Pneumography	
Confirmation of clinical diagnosis	15
"Normal"	2
Not done	4
Shunt	4
Craniotomy	2
Location	
Pons	16
Brain stem	4
Medulla	1

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had confirmed the presence of a lesion in 15, had shown no abnormality in 2, and had not been performed in 4 patients. At the time of diagnosis, 18 of the 21 patients were 20 years or less of age. A shunt of the cerebral spinal fluid system had been performed in 4 patients and operative decompression in 2. The small number of operative shunts or decompressions is probably related to the low incidence of significant obstruction caused by tumors in this area.

Radiation therapy was given through 2 or 3 fields. With occasional exceptions, treatment was at the rate of 600 to 800 r calculated tumor dose per week. Before 1945, only 2 of the 10 patients received a dose higher than 2,600 r. Those treated in 1945 or later received doses ranging from 3,300 to 5,000 r.

Within a few weeks after completion of therapy, 15 of the 21 patients experienced definite improvement (Table II), but 10 of these showed recurrence within 7 months and were dead within 15 months. The 6 failing to respond to treatment died within 6 months.

Of the 5 patients surviving more than 5 years, 4 are living at 6, 12, 13½, and 22 years after treatment. These 4 have had excellent recoveries. After about 6 years, the fifth patient began to deteriorate slowly and 12 years after irradiation died of a cystic astrocytoma. Each of these 5 patients who survived 5 years had received a radiation dose of at least 3,300 r, preceded by either operative decompression or shunt.

TABLE II

GROUP I. PONS, MEDULLA, AND BRAIN STEM
RESULTS OF RADIATION THERAPY

Result	No. of Patients
Initial improvement	15
Recurred, died 15 mo.	10
5 year survivors	
Still living (6, 12, 13½, 22 yr.)	4
Recurred 6 yr., died 12 yr. (astrocytoma)	1
No response; died 6 mo.	6

TABLE III

GROUP I. PONS, MEDULLA, AND BRAIN STEM
HISTOLOGIC DIAGNOSIS

Histologic Diagnosis	No. of Patients	Survival Time
Glioblastoma multiforme	3	5-15 mo.
Polar spongioblastoma	3	2-9 mo.
Cystic astrocytoma	2	3 mo.; 12 yr.
Fibrillary astrocytoma	1	5 mo.
Medulloblastoma	1	1 mo.
Neuroblastoma	1	2 mo.
Epidermoid cyst	1	2 mo.

Necropsies were done in 12 cases (Table III) and revealed 3 instances of glioblastoma multiforme, 3 of polar spongioblastoma, 2 of cystic astrocytoma, and 1 each of fibrillary astrocytoma, medulloblastoma, neuroblastoma, or epidermoid cyst.

GROUP II. LESIONS OF THE MESENCEPHALON,
THE PINEAL REGION AND THE WALLS
OF THE THIRD VENTRICLE

All 17 patients in this group had definite pneumographic as well as clinical evidence of a tumor in the area of concern (Table IV). Ten patients were 20 years of age or younger. Exploratory craniotomy had been performed in 3 and cerebrospinal fluid shunts in 9 others. The larger proportion of shunts performed in Group II than in

TABLE IV

GROUP II. MESENCEPHALON, PINEAL, AND WALL OF
THIRD VENTRICLE
COMPOSITION OF SERIES

No. of patients	17
Less than 20 years of age	10
Pneumography	
Confirmation of clinical diagnosis	17
Craniotomy	3
Shunt	9
Location	
Posterior third ventricle	9
Walls of third ventricle	7
Mesencephalon	1

TABLE V
GROUP II. MESENCEPHALON, PINEAL, AND WALL OF
THIRD VENTRICLE
RESULTS OF RADIATION THERAPY

Result	No. of Patients
Initial improvement	10
Recurred, died 24 mo.	5
5 year survivors	
Still living (5, 7, 20, and 24 yr.)	4
Recurred 9 yr., died 10 yr.	1
No response	7
Died 16 mo.	5
No change 10 yr.	1
No change 5 yr., then recurred*	1

* Intraventricular epidermoid cyst—lost to follow-up after operative removal.

Group I reflects a higher incidence of block of the cerebrospinal fluid pathway.

The arrangement of treatment fields was similar to that used in Group I. Radiation therapy was usually given at the rate of 600 to 800 r calculated tumor dose per week. Fourteen of the 15 patients who completed the course of therapy received tumor doses of 3,200 to 6,000 r. The other 2 patients were terminal at the start of treatment and died before therapy was completed.

Prompt, marked improvement was noted in 9 patients (Table v) and definite but limited improvement in 1 other. One patient has remained unchanged for 10 years and another was unchanged until signs of reactivation appeared 5 years later. The 5 patients who failed to respond to treatment died within 16 months. In total, 7 of the 17 patients survived 5 years or longer and 5 of these remain without evident recurrence for periods of 5, 7, 10, 20, and 24 years. In the 2 others, signs of renewed tumor growth developed after 5 and 9 years.

The 7 survivors of 5 or more years include 1 patient with previous exploratory craniotomy and 4 with shunts (Table x). Two underwent no operative procedure.

As in Group I, the deaths tended to occur

early. Of the 11 deaths, 10 were within 2 years of treatment.

Postmortem examination (Table vi) in 6 cases and craniotomy for a recurrence in a seventh patient showed 2 intraventricular epidermoid cysts, 1 polar spongioblastoma, 3 astrocytomas, and 1 papilloma of the choroid plexus.

GROUP III. LESIONS OF THE CEREBELLUM AND
THE ROOF OF THE FOURTH VENTRICLE

This group consists of 23 patients (Table vii) all of whom were treated before January, 1949. Previous to 1949, following the suggestion of Cutler, Sosman, and Vaughan,⁸ approximately half of all patients in this clinic with the presumptive diagnosis of medulloblastoma were given radiation therapy without biopsy or attempted removal. This accounted for 18 of the patients in Group III. Three patients were irradiated without biopsy because of the operative finding of a highly vascular tumor. In the other 2 patients craniotomy had failed to disclose the lesion indicated clinically and by pneumography. That there has been no patient added to this group during the last 15 years reflects primarily the change in opinion regarding exploration for medulloblastoma.

Previous to radiation therapy, 10 patients of this group had had decompression by either posterior craniotomy or placement of a catheter into a lateral ventricle.

Only 3 patients in this group were older

TABLE VI
GROUP II. MESENCEPHALON, PINEAL, AND WALL
OF THIRD VENTRICLE
HISTOLOGIC DIAGNOSIS

Histologic Diagnosis	No. of Patients	Survival Time
Epidermoid cyst		
(intraventricular)	2	22 mo.; 6 yr.*
Polar spongioblastoma	1	16 mo.
Gemistocytic astrocytoma	1	7 mo.
Malignant astrocytoma	2	1 mo.; 10 mo.
Papilloma choroid plexus	1	9 mo.

* Alive when lost to follow-up at 6 years.

TABLE VII

GROUP III. CEREBELLUM AND ROOF OF FOURTH
VENTRICLE
COMPOSITION OF SERIES

No. of patients		23
Less than 17 years of age	20	
Pneumography		
Confirmation of clinical diagnosis	10	
Not done	13	
Craniotomy	7	
Shunt	3	
Location		
Cerebellum	10	
"Posterior fossa"	11	
Fourth ventricle	2	

than 16 years. Each of these 3 had had craniotomy and the lesion was either not found or was too vascular for biopsy. In these 3, a meningioma, a neurofibroma, and a cerebellar hemangioblastoma were proved subsequently. These patients appear to differ from the other 20 in Group III in terms of age, reason for treatment without biopsy, and ultimate diagnosis.

The remainder of this discussion will be limited to the 19 patients less than 10 years of age and the 1 aged 16 (Table VIII). The group thus becomes more homogeneous and consists largely of those considered at the time of treatment as probable medul-

TABLE VIII

GROUP III. CEREBELLUM AND ROOF OF FOURTH
VENTRICLE
DIAGNOSIS IN PATIENTS LESS
THAN 17 YEARS OF AGE

Diagnosis	No. of Patients
Presumptive diagnosis	
Medulloblastoma	18
Too vascular	2
Histologic diagnosis	
Medulloblastoma	4
Astrocytoma	6
"Encephalitis"	1
Unknown	9

TABLE IX

GROUP III. CEREBELLUM AND ROOF OF FOURTH
VENTRICLE
RESULTS OF RADIATION THERAPY IN PATIENTS
LESS THAN 17 YEARS OF AGE

Results	No. of Patients
Initial improvement	15
Recurred, died 28 mo.	8
5 year survivors	7
Still living (12, 23, 26, 27 yr.)	4
Recurred, irradiated, died (7 yr.)*	1
Recurred, operated, living (16 yr.; 28 yr.†)	2
No response	5
Died, 4 mo.	4
Operated on, living (16 yr.†)	1

* Medulloblastoma.

† Astrocytoma.

loblastomas. Although the clinical evidence of a tumor in each of the 20 patients was substantial, confirmatory pneumographic studies were carried out in only 8. Subsequent operation or postmortem examination in 11 resulted in the final diagnosis of medulloblastoma, 4; astrocytoma, 6; and diffuse "encephalitis," 1.

All 20 patients received radiation therapy to the posterior fossa. In addition, radiation was given to the cervical spine in 11 and to the thoracic and lumbar spine in 3. With 2 exceptions, tumor doses to the primary site were calculated to be between 2,000 and 4,000 r, given at the rate of 600 to 1,000 r per week.

A prompt, marked improvement in 13 patients and a slight transient improvement in 2 others were noted (Table IX). Of these 15, 8 died of recurrence within 28 months and 1 died of recurrent medulloblastoma after 7 years. Two patients operated on 10 and 15 years later had astrocytomas and are currently well after total periods of 16 and 28 years. Four of the 15 patients showing improvement are living without further therapy at 12, 23, 26, and 27 years after treatment.

Of the 5 patients who initially failed to respond to treatment, 4 were dead within 4 months. The fifth had a fibrillary astrocytoma removed surgically 4 weeks after completion of radiation therapy and is now without neurologic deficit some 16 years later. Thus, there were eight 5 year survivors, but 1 died at 7 years of recurrence and 3 patients with astrocytomas were salvaged by operative procedures.

DISCUSSION

Groups I and II combined contain a total of 38 patients with clinical evidence of an intracranial lesion in the pons, medulla, mesencephalon, pineal area, or walls of the third ventricle. The clinical diagnosis was confirmed by pneumographic studies in 32 of the 38. Because attempt at removal or biopsy of these lesions was considered excessively hazardous, they were treated with roentgen therapy without preliminary biopsy. About half of these patients (18) also received some type of operative decompression. Rapid and often complete relief of symptoms and neurologic findings was obtained in 25 patients (66 per cent). However, many recurred within a few weeks or months. Within 2 years of diagnosis, 26 of 38 patients had died of their brain tumor.

There were 12 (32 per cent) 5 year survivors. Of these, 1 was lost to follow-up at 6 years and 2 died of recurrence at 10 and 12 years. Still under observation are 9 without evidence of recurrence at 5, 6, 7, 10, 12, 13½, 20, 22, and 24 years (Table x). Of the 9, 8 are leading essentially normal lives without significant neurologic deficit from the tumor or the treatment. With 1 exception, these 9 received calculated tumor doses of between 4,000 and 6,000 r (Table x). Since several of the patients with poorer prognosis were given the lesser doses, definite conclusions regarding the optimum dose cannot be drawn from these data. However, because most of the successfully treated patients did receive doses of between 4,000 and 6,000 r, and these doses are relatively safe, we are now treating with doses of about 5,000 r.

Although the histologic diagnosis was uncertain in all but 1 of the current survivors of Groups I and II, the clinical evidence of a space-occupying lesion was, in general, convincing. Furthermore, in 11 of the 12 5 year survivors, the clinical evidence was supported by pneumographic findings. Thus, we may assume that these patients did, in fact, have brain tumors.

How much of the improvement that fol-

TABLE X
GROUPS I AND II. 5 YEAR SURVIVORS

Patient	Tumor Location	Pneumography	Decompression	Tumor Dose (r)	Status (yr.)
I—5	Brain stem	Not done	Yes	4,400	Living (22)
I—11	Brain stem	+	Yes	3,300	Died (12)
I—14	Medulla	+	Yes	4,000	Living (13½)
I—16	Brain stem	+	Yes	4,400	Living (12)
I—21	Pons	+	Yes	4,900	Living (6)
II—1	Pineal area	+	No	6,000	Living (24)
II—3	Floor, 3rd ventricle	+	No	3,100	Living (20)
II—7	Posterior, 3rd ventricle	+	Yes	5,500	Died (10)
II—8	Optic chiasm	+	Yes	4,300	Living (10)
II—11	Pineal area	+	Yes	5,000	Living (7)
II—12	Pineal area	+	Yes	3,000*	Lost; alive (6)
II—15	Thalamus	+	Yes	5,000	Living (5)

"+" means that pneumography confirmed clinical information.

* Recurred at 5½ years and then operated on.

TABLE XI

GROUP III. 5 YEAR SURVIVORS IN PATIENTS LESS THAN 17 YEARS OF AGE

Patient	Pneumog- raphy	Decompres- sion	Retreatment	Histologic Diagnosis	Status (yr.)
III—2	Not done	No	Operative	Fibrous astrocytoma	Living (28)
III—3	Not done	No	None	—	Living (27)
III—6	Not done	No	None	—	Living (26)
III—13	Not done	No	None	—	Living (23)
III—15	Not done	No	None	—	Living (12)
III—16	+	Yes	Roentgen irradiation	Medulloblastoma	Dead (7)
III—21	+	Yes	Operative	Fibrous astrocytoma	Living (16)
III—22	+	Yes	Operative	Fibrous astrocytoma	Living (16)

"+" means that pneumography confirmed clinical information.

lowed therapy should be ascribed to mechanical relief of pressure or to radiation therapy is uncertain. Of the 5 year survivors, 2 had undergone no operative procedure for relief of pressure. In the other 10, 7 shunts and 3 exploratory craniotomies had been done.

The beneficial responses to therapy were about equally distributed between Groups I and II. These results are comparable to those reported elsewhere.^{1,2,4,5,6}

In that the lesions of patients of Group III could have had biopsy and in some cases been resected, they present a different problem. The question here is whether the type of treatment might have been better selected, planned, and executed had biopsy first been performed. Although 8 of the 20 patients considered in this group survived 5 years or longer (Table XI), in only 1 of the 8 was the clinically suspected medulloblastoma proved. This patient, following treatment for spinal cord involvement 2 years after the initial irradiation, died of recurrence at 7 years. Three patients with astrocytomas survived from 16 to 28 years, but all 3 required operative removal because of radiation failure. The 4 patients alive without further therapy for periods of 12 to 27 years had neither pneumographic nor angiographic studies to support the clinical diagnosis. Thus, of the 8 patients surviving at least 5 years with suspected lesions in the cerebellum or the roof of the fourth ventricle, 4 required retreatment

and in the other 4 the diagnosis was unsupported by roentgenographic studies. Re-stated, primary radiation therapy in this group was successful only in the cases where the diagnosis of a tumor was least certain. Currently, we believe that, whenever possible, biopsy of suspected lesions of the cerebellum or the roof of the fourth ventricle is preferable to treating on the presumptive diagnosis of medulloblastoma. Then, if the lesion is one that should be treated by surgical means, such can be done without delay. On the other hand, if the lesion proves to be a medulloblastoma with its known tendency to seed throughout the cerebrospinal fluid space, radiation therapy can be planned accordingly.

SUMMARY AND CONCLUSIONS

A high mortality is associated with surgical procedures for tumors of the brain stem (including pons and medulla) and the pineal-third ventricle regions. For this reason, 38 patients with such tumors were treated by radiation without biopsy. Early favorable response occurred in 15 of 21 of those with tumors in the brain stem and in 10 of 17 with tumors in the pineal third ventricle area. In the first group, 5 of the 21 patients and in the second group 7 of the 17 patients survived 5 years or longer. Of these 12 survivors, 9 have been without evidence of recurrence for periods of up to 24 years. Our present opinion is that with such tumors, patients should be given radiation

therapy; that biopsy is not necessarily required; and that decompression should be used when necessary for rapid relief of intracranial pressure.

Lesions of the cerebellum and roof of the fourth ventricle, however, should have biopsy and therapy planned according to the result thereof.

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EMBRYONAL RHABDOMYOSARCOMA*

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WHILE embryonal rhabdomyosarcoma as a specific entity is not a common tumor, during the past decade it has been recognized among clinicians and pathologists alike as the most common form of tumor of striated muscle origin. Lawrence and his group⁹ reported on 48 cases, exclusive of primary lesions of the head and neck over a 24 year period (1934-1959) at the Memorial Center for Cancer and Allied Diseases, New York City. Stobbe and Dargeon¹⁶ reported their experiences with 15 cases over a 19 year period (1931-1949), and over the next 7 years Moore and Grossi¹⁰ reported 37 cases, also at the Memorial Center. Both of these latter series were cases involving the head and neck region. Dito and Batsakis⁵ reviewed 161 cases reported in the American and English literature and added their observations on 9 additional cases of rhabdomyosarcoma arising in the head and neck region and treated at Walter Reed General Hospital.

The relative lack of radiotherapeutic details pertaining to radiosensitivity, as well as the somewhat divergent opinions in the oncologic literature concerning local radio-curability, and the paucity of such information in the radiologic literature have stimulated us to report our series. Twenty patients with embryonal rhabdomyosarcoma treated in the Radiation Therapy Section of Walter Reed General Hospital, Washington, D. C., during the period July, 1956 to July, 1963, comprise this series. The histologic diagnosis of embryonal rhabdomyosarcoma was confirmed by our pathology staff.

HISTORICAL NOTE

The first reported case of what was probably a rhabdomyosarcoma appeared

in 1854 when Weber described a localized enlargement of the tongue of a 21 year old man.¹⁷ This was excised but later recurred. It was made up of striated muscle cells in all stages of differentiation from adult to embryonal forms. Other case reports in the literature, not all of which are verified, were by Billroth (1850), Buhl (2 cases, 1865), Ribbert (2 cases, 1891), and Bayer (orbit of child, 1882).¹¹ The first large series of cases of rhabdomyosarcoma was reported by Rakov¹⁵ in 1937. In 1943 Nettleship in the *Journal of the National Cancer Institute* described a spontaneous transplantable, mature type of rhabdomyosarcoma in strain C mice.¹¹ This tumor was similar to such tumors in man, but contained a more adult type of cells with intact cross-striations and myofibrils. In 1946 Stout¹⁷ presented a clinicopathologic study of 121 cases. Subsequent series of cases have been reported by Pack and Eberhardt,¹¹ Horn and Enterline,^{7,8} Phelan and Juado,¹³ Dito and Batsakis,^{5,6} Albores-Saavedra *et al.*,¹ and Patton and Horn.¹² The various types of rhabdomyosarcoma occurring in childhood have been the subject of reports by Areán and Marcial-Rojas,² Pinkel and Pickren,¹⁴ Bowman,⁴ and Bailey *et al.*³

GROSS APPEARANCE

The gross appearance of embryonal rhabdomyosarcoma reveals little in the way of characteristic findings except for the botryoid variant. Most arise in muscle; however, a few of the nonbotryoid tumors arise where striated muscle does not ordinarily occur, *i.e.*, the distal phalanx of the thumb and mandible. The color may be white, reddish-pink or red. The consistency varies from soft to firm depending on the amount of collagen present. The presence of

* From the Radiology Service, Walter Reed General Hospital, Washington, D. C. This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any endorsement of the opinions advanced or any recommendation of such products as may be named.

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poorly demarcated, soft yellow regions or cysts is the result of degeneration or necrosis. There is great variation in tumor size. The botryoid tumors have an appearance similar to myxomatous, edematous polyps. In the palate or nasopharynx, the mucosa overlying the tumor is bulging, and often there is a poorly defined ulcer with a granular base or a fungating, granular mass. Stobbe and Dargeon¹⁶ warn that some of the tumors within skeletal muscle may give a false appearance of circumscription or encapsulation.

MICROSCOPIC APPEARANCE

The classification of rhabdomyosarcomas used in this series is the one outlined by Horn and Enterline⁸ in 1958. The tumors are broken down into 4 categories: pleomorphic, alveolar, embryonal, and botryoid. Microscopically, the pleomorphic variety is relatively pure and is found mainly in older adults. The other 3 types often intermix and occur mainly in children and young adults.

The pleomorphic type is principally a spindle cell tumor and usually contains little collagen. Its cellularity and pleomorphism distinguish it from a fibrosarcoma. Strap-like or ribbon-shaped cells are present which have bright eosinophilic cytoplasm. Some are multinucleated. Longitudinal myofibrils or cross-striations may be seen, but these are not necessary to make the diagnosis.

The alveolar type shown in Figure 1 is characterized by "alveoli" separated by connective tissue trabeculae of varying vascularity. One or more layers of cells are usually applied to the trabeculae. The center of each alveolus appears empty except for varying numbers of freely floating cells unattached to one another. Single or multinucleated giant cells may be present, and longitudinal or cross-striations may be seen in these or in smaller cells. Some tumors show a narrow foot between trabeculae and cells adjacent to them suggesting that many of the trabeculae are really giant muscle fibers with the nuclei situated in

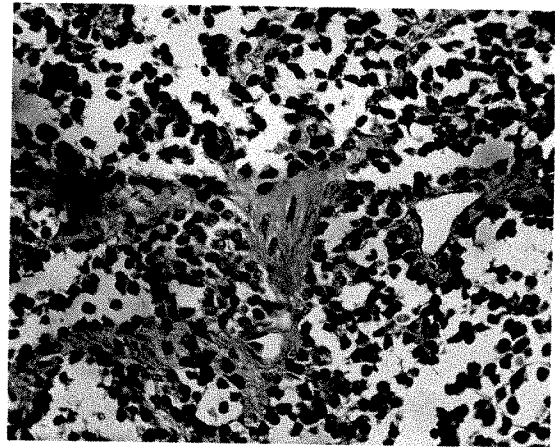


FIG. 1. Alveolar rhabdomyosarcoma.

lateral cytoplasmic extensions. Varying degrees of pleomorphism may be seen. One of our cases contained solid embryonal areas.

In the embryonal variety the basic cell type is long, slim and spindle-shaped, tapering to thin bipolar processes. There is usually a single, central nucleus and abundant eosinophilic cytoplasm. Some of these are seen under low power in Figure 2. Longitudinal myofibrils may be present. Cross-striations may also be seen as shown in Figure 3. Sometimes these cells are enlarged about the nucleus, and, when the nucleus is near one end, the cell may have a tadpole shape. At times, the tumor may have a myxoma-like appearance with small

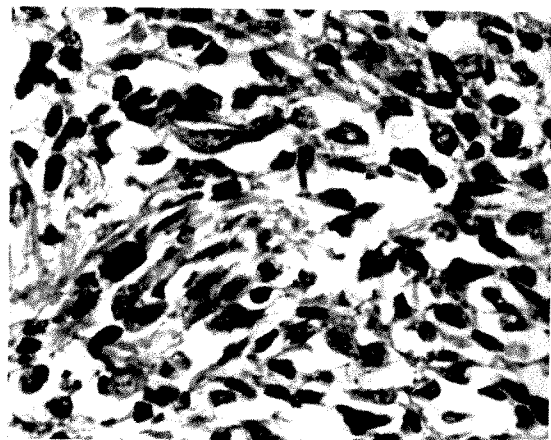


FIG. 2. Embryonal rhabdomyosarcoma showing loosely arranged spindle cells.

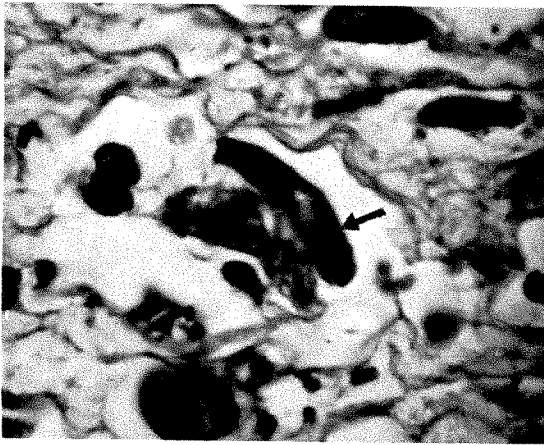


FIG. 3. Embryonal rhabdomyosarcoma showing cross-striations.

cells. Small or large round cells may also be present as shown in Figure 4. Two of our cases contained giant cells. In a few instances they were multinucleated, and some of the cells were fused into a syncytial mass. One of our cases contained elements of leiomyosarcoma, neurofibrosarcoma, and fibrosarcoma.

The botryoid type resembles the embryonal variety microscopically but differs in gross appearance and location. Typical locations include the nasopharynx, middle ear, maxillary sinus, genitourinary tract, and common bile duct. The primary lesions are polypoid, edematous, centrally hypocellular, and covered by normal mucous mem-

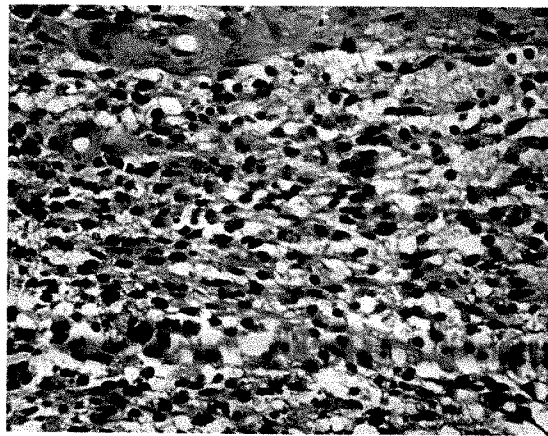


FIG. 5. Botryoid rhabdomyosarcoma.

brane at the site of origin. A characteristic feature, which may or may not be seen, is the "cambium layer" of Nicholson. This is a multilayered band of short spindle cells with relatively little cytoplasm lying parallel to the mucosal surface of the tumor just beneath the mucosa. These have shown a high rate of mitotic activity. A low-power view of the botryoid type is shown in Figure 5, and the "cambium layer" of Nicholson in Figure 6.

Cross-striations are helpful but not essential in diagnosing any of the types of rhabdomyosarcoma. Normally developing striated muscle, corresponding to the stages of embryonal and alveolar rhabdomyosarcoma, frequently does not have cross-stria-

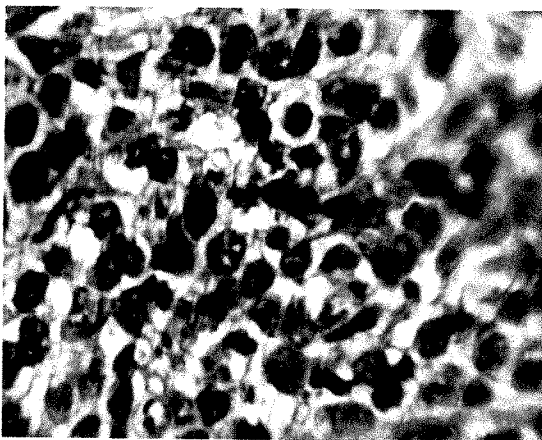


FIG. 4. Embryonal rhabdomyosarcoma showing round cells.

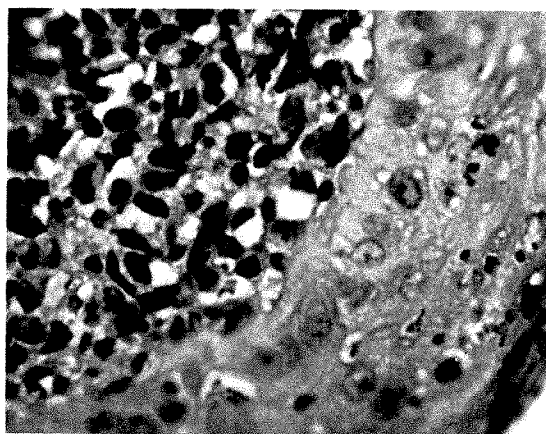


FIG. 6. Botryoid rhabdomyosarcoma showing "cambium layer" of Nicholson.

tions. Hence their absence in these tumors may be expected. In 1962 Patton and Horn¹² reported a study of muscle from the arm and thigh of 16 human embryos and fetuses. An attempt was made to correlate the morphology of developing muscle with that of rhabdomyosarcoma. Embryonal rhabdomyosarcoma closely resembled developing muscle in the 7 to 10 week fetus, and the alveolar pattern resembled developing muscle at 10 to 12 weeks. The presence of alveolar and embryonal areas together in some of the tumors was a reflection of a similar finding in fetal muscle. Cross-striations were present at 10 weeks but were not prominent until 14 weeks. In contrast, the authors felt that the pleomorphic rhabdomyosarcoma with its pattern of marked cellular variation and absence of any resemblance to developing muscle suggested a product of dedifferentiation of adult striated muscle.

Since in essence the botryoid and alveolar types are felt to be subvariants of the embryonal rhabdomyosarcoma, we included in our series only the alveolar, embryonal, and botryoid types of rhabdomyosarcoma. Because of the difference in the age group, difference in clinical activity and therapeutic response, as well as the histologic differences, examples of the pleomorphic variety were omitted. Likewise, because of certain clinical and pathological criteria which separate them from the over-all group, cases of sarcoma botryoides of the genitourinary tract (prostate, uterus, bladder, vagina) were not included in this study.

In our series an original diagnosis of embryonal rhabdomyosarcoma or one of its subtype variants was made in 12 instances. The other 8 cases included incorrect original diagnoses of hemangiosarcoma, undifferentiated sarcoma, undifferentiated malignant mesenchymoma, lymphoepithelioma, anaplastic carcinoma, and reticulum cell sarcoma. More frequent recognition and reporting of embryonal rhabdomyosarcoma will occur as clinicians and pathologists become more aware of its existence and the criteria required for its diagnosis.

CLINICAL FINDINGS

Age, Sex and Race. Our 20 cases were rather equally divided between children and adults, 12 being under age 11. The ages at diagnosis for the 8 adults varied from 19 to 67 years, with a mean age of 30 years. The tumor appeared at 18 months of age in our youngest patient. Our series is thus more heavily weighted with adult patients than the series of Moore and Grossi,¹⁰ and Lawrence *et al.*⁹ The over-all sex distribution showed a slight preponderance of males (11 to 9) over females, which corresponds with the findings of other observers. Three of our patients were Negroes.

Anatomic Distribution. The anatomic distribution of the primary tumors in our series is best illustrated by the schematic diagram in Figure 7.

The distribution of the primary tumors in these patients falls roughly into 4 ana-

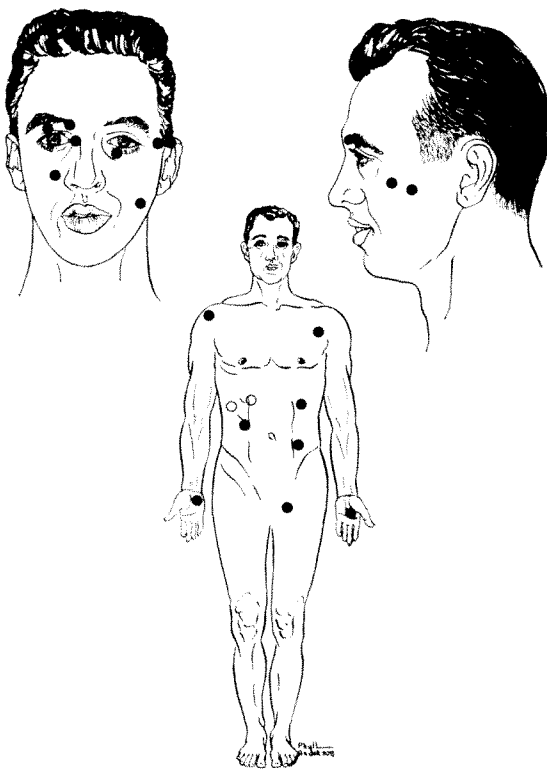


FIG. 7. Schematic representation of anatomic distribution of cases of embryonal rhabdomyosarcoma in the present series. Open circles represent liver primary lesions.

TABLE I
HISTOLOGIC TUMOR SUBTYPE BY
ANATOMIC LOCATION

Site	Embry- onal	Botry- oid	Alveo- lar	Total
Head and Neck	7	2	1	10
Retroperitoneal	3	0	0	3
Extremity and Torso	3	0	2	5
Liver	1	1	0	2
Total	14	3	3	20

tomic groups (Table I): (1) the head and neck region (10 patients); (2) retroperitoneal region (3 patients); (3) extremities and torso (5 patients); and (4) the liver (2 patients). In contrast to the sex relationship reported by Lawrence *et al.*,⁹ all our retroperitoneal cases were in females and all our extremity cases were in males (Table II). The preponderant tumor was the embryonal rhabdomyosarcoma but the alveolar variant was noted in 3 cases and the botryoid variant also in 3 instances (Table I).

Symptoms. The most common symptom associated with embryonal rhabdomyosarcoma was the presence of a mass, noted in 13 of our 20 patients. This was uniformly true in our patients with extremity and torso (girdle) primary lesions and in 7 of the 10 patients with head and neck primaries (Table III). Pain as a presenting symptom was encountered in only 4 of our cases (2 of

the 3 with retroperitoneal primary tumors); 1 head and neck case presented because of a pulmonary lesion, and 1 case with a liver primary tumor because of obstructive jaundice.

The mean interval between initial symptoms and pathologic diagnosis was 3.5 months for the entire group (Table IV) and interestingly enough the mean interval for both the head and neck and retroperitoneal tumors was 3.7 months. This relatively long waiting period for the head and neck lesions may be related to the fact that in 5 patients the lesions were located in the nasopharynx, maxillary antrum or nasal cavity. The uniform failure in treatment of large retroperitoneal primary lesions is, in general, the experience of others, which further supports the concept of a relatively "silent period" of significant initial growth in this location.

Physical Examination. The major physical finding in our patients was the presence of an abnormal mass. The presence of regional lymphatic involvement at initial examination was uncommon. One patient with a head and neck (temporal) primary lesion had initial neck lymph node involvement which was proven to contain metastatic disease (Table V); also 1 patient with a retroperitoneal primary lesion had metastases to iliac and abdominal lymph nodes (surgically). During the course of clinical evaluation after diagnosis, however, 6 cases proved to have clinical lymph node involvement. In 1 head and neck case metastatic

TABLE II
SEX OF PATIENTS AND ANATOMIC LOCATION OF PRIMARY TUMOR

Site	Male			Female		
	Living	Dead	Total	Living	Dead	Total
Head and Neck	1	5	6	0	4	4
Retroperitoneal	0	0	0	0	3	3
Extremity and Torso	3	2	5	0	0	0
Liver	0	0	0	2	0	2
Total	4	7	11	2	7	9

TABLE III
RELATIONSHIP OF FIRST SYMPTOM NOTED TO ANATOMIC SITE OF PRIMARY TUMOR

Site	No. of Patients	Mass	Pain	Pulmonary Metastases	Other
Head and Neck	10	7	1	1	1
Retroperitoneal	3	1	2	0	0
Extremity and Torso	5	5	0	0	0
Liver	2	0	1	0	1
	20	13	4	1	2

esions to the thoracic vertebrae were noted and treated before death. A pulmonary metastasis was noted initially in 1 case, and 1 case had liver metastases. Subsequently, 6 patients were known to have pulmonary metastases, and 3 prior to death had liver metastases. The autopsy findings in 10 of our 14 deceased patients are presented in Table v. The central nervous system involvement was minimal. Two cases revealed epidural metastases with cord compression at autopsy.

Seventeen of our cases exhibited a rapid or aggressive growth pattern, either in terms of growth of the primary lesion or subsequent metastases. Three of our cases

had a more indolent growth pattern (2 patients with head and neck and 1 with extremity primary lesions).

TREATMENT

The 20 patients in this series were all treated in the radiotherapy department, either for the primary tumor or for metastases. Thirteen of our cases had received prior definitive therapy of a surgical nature (more than biopsy for diagnostic purposes). This is summarized in Table vi. Surgery included attempted initial total excision or extirpation in 8 cases, and partial excision or palliative surgery in 5 cases. Two cases were operated on after initial radiation therapy, 1 with a curative intent and 1 for palliation. In 15 patients primary sites were irradiated with a locally curative intent and in 2 with a palliative intent. In 12 cases, metastatic sites were irradiated.

Over-all treatment consisted of irradiation alone in 5 cases, and irradiation, surgery, and chemotherapy in various combinations in the remainder. In none of our cases was there an appreciable delay between a definitive pathologic diagnosis and the institution of some form of therapy.

Eleven of 20 patients received systemic chemotherapy at some time during their course. The agents employed and their responses are listed in Table vii. Only 3 significant responses were obtained, 1 in a head and neck primary lesion with actinomycin D and 2 in liver primary lesions with vincristine. It should be pointed out, however, that chemotherapy was usually not

TABLE IV
INTERVAL BETWEEN FIRST SYMPTOM AND
DIAGNOSIS AND TREATMENT

Site	No. of Patients	Mean Interval (mo.)
Head and Neck	10	3.7
Living	1	8.0
Dead	9	3.1
Retroperitoneal	3	3.7
Living	0	0
Dead	3	3.7
Extremity and Torso	5	3.4
Living	3	4.3
Dead	2	2.0
Liver	2	2.5
Living	2	2.5
Dead	0	0

TABLE V
INCIDENCE AND SITES OF KNOWN METASTATIC LESIONS IN 14 DEAD PATIENTS

Metastases Present	No. of Patients	Site				
		Central Nervous System	Lung	Liver	Lymph Nodes	Bone
At time of primary treatment	4	0	1	1	2	0
Later in course	7	1	6	3	6	1
At autopsy*	10	2	9	6	8	3

* Four cases were not autopsied.

TABLE VI
SUMMARY OF TREATMENT BY ANATOMIC SITE*

Primary Site	No. of Patients	Surgery Initially†	Curative Irradiation	Palliative Irradiation	Irradiation for Metastases
Head and Neck	10	5	8	1	4
Retroperitoneal	3	3	3	0	4
Extremity and Torso	5	5	3	0	4
Liver	2	0	1	1	0
	20	13	15	2	12

* In addition, 11 patients received chemotherapy.

† More than biopsy for diagnostic purposes.

employed initially, and most of the patients at the time of institution of chemotherapy were poor candidates for evaluation, and had evidence of rather advanced disease, usually with metastatic spread. One case of liver primary lesion (embryonal) was given only one palliative tumor dose of 300 and then was placed on vincristine, due to evidence of disseminated disease. She has striking clinical evidence of marked regression, and, although the prognosis is, of course, very grave, her response to this agent has been very dramatic.

The most commonly used agent was actinomycin D. Reports by Pinkel and Pickren¹⁴ and Tan *et al.*¹⁸ suggest significant benefit with this agent in some cases, when employed for palliative therapy. Only 1 out of 5 of our cases showed a significant clinical response to this agent.

RESULTS OF TREATMENT

Fourteen of our patients are now deceased. The mean survival time from treat-

ment (institution of initial) for all patients was 10.3 months. Those with head and neck lesions had a mean survival time of 11 months, those with retroperitoneal lesions 9.3 months, and those with lesions of the extremities 9.0 months (Table VIII). A summary of the treatment plans in the living cases is presented in Table IX, and a summary of the deceased cases in Table X.

TABLE VII
TYPE OF CHEMOTHERAPY RECEIVED BY 11 OF 20 PATIENTS

Agent	No. of Patients	Significant Response
Actinomycin D	5	1
Nitrogen Mustard	1	0
Metasarcolysin	1	0
Cytosan-Metacorten	1	0
Vincristine	2	2
Vinleukoblastin	1	0
	11	3

TABLE VIII
SURVIVAL TIME (TREATMENT TO DEATH) IN
14 DECEASED PATIENTS

Site	No. of Patients	Mean Survival (mo.)
Head and Neck	9	11.0
Retroperitoneal	3	9.3
Extremity and Torso	2	9.0
Total	14	10.3

There were no long-term survivors, but considering the aggressive nature and usual behavior and outcome of embryonal rhabdomyosarcoma, we do not feel that the reporting of such a series need be delayed for a 5 year survival group.

The 2 patients with liver primary lesions are living at 10 months with rather striking chemotherapeutic responses to vincristine, added after radiation therapy (palliative irradiation in 1 instance) (Table IX). The prognosis is, of course, very guarded, but at present, they are healthy, gaining weight, and show no evidence of jaundice or systemic disease. One patient is alive without evidence of disease who had head and neck involvement (a botryoid primary lesion of the nasopharynx) 36 months after definitive treatment by irradiation of the primary tumor, followed by actinomycin D and radiation therapy of an apparently solitary lung metastasis, 4 months after treatment of the primary lesion.

Three cases with extremity and girdle (torso) lesions are living. In 1 (S.D.) the primary tumor was treated surgically and an apparently solitary pulmonary metastatic lesion was irradiated to a tumor dose of 6,000 r.

The autopsy findings have been previously referred to in 10 of our 14 deceased patients (Table V). In addition to the more common tabulated sites (regional and distant lymph nodes, lung, liver, bone, central nervous system), other sites of metastasis were: kidney (2), soft tissues (2), spleen

TABLE IX
TREATMENT PROGRAM OF SURVIVING PATIENTS

Patient	Age (yr.)	Race and Sex	Tumor and Subtype	Primary Site	Interval between Symptoms and Treatment (mo.)	Survival Time (mo.)	Initial Treatment	Subsequent Treatment	Chemotherapy	Area Irradiated	Treatment Factors (mm. hv; tumor dose [r]; days)	Regression	Control	Present Status
R.S.	11	W M	Botryoid	Nasopharynx	8	36	Irradiation	Irradiation	Actinomycin D	Nasopharynx Lung metastasis	9 Pb—6,000—52 7 Pb—5,000—39	Yes Yes	Yes	No complications No evidence of disease
W.B.	53	W M	Embryonal	Left thigh	9	18	Surgery	Irradiation	Actinomycin D	Lung metastasis Pelvic mass	9 Pb—5,100—47 7 Pb—6,000—45	Yes Yes	Yes	No complications No evidence of disease
S.D.	22	W M	Embryonal	Right shoulder	2	28	Surgery	Irradiation	None	Lung metastasis	9 Pb—6,000—30	Yes	Yes	No complications No evidence of disease
J.A.	3½	W M	Alveolar	Left shoulder	2	8	Surgery	Irradiation	None	Left shoulder	7 Pb—5,000—38	Yes	Yes	No complications No evidence of disease
L.J.	2	W F	Embryonal	Liver	3	8	Irradiation	—	Vincristine	Liver	9 Pb—300—1	No	No	Disseminated disease
T.H.	4½	N F	Botryoid	Liver	2	10	Irradiation	—	Vincristine	Liver	9 Pb—4,000—30	Yes	No	Marked regression with vincristine, no symptoms or clinical evidence of disease

TABLE X
TREATMENT PROGRAM OF DECEASED PATIENTS

Pa- tient	Age (yr.)	Race and Sex	Tumor Subtype	Primary Site	Interval between Symptoms and Treatment (mo.)		Initial Treatment	Subsequent Treatment	Chemotherapy	Area Irradiated	Treatment Factors (mm. hvl; tumor dose [r]; days)	Regres- sion	Local Control	Course	
D.D.	4	W	F	Embryonal	Right orbit	2	5	Surgery	Irradiation	None	Right orbit	7 Pb—5,000—37	Yes	No	Died with disseminated disease
C.C.	4	W	M	Embryona	Angle of left mandible	2	10	Surgery	Irradiation	None	Angle of left mandible	3.7 Pb—4,500—37	Yes	No	Died with disseminated disease
F.T.	67	W	F	Embryonal	Retropertitoneal	6	14	Surgery	Irradiation	Metasarcolysin	Retropertitoneal	9 Pb—4,200—26	Yes	No	Died with disseminated disease
I.A.	28	W	M	Embryonal	Left orbit and antrum	11	10	Surgery	Irradiation	Actinomycin D	Left orbit and antrum Dorsal spine	7 Pb—7,200—39 7 Pb—3,350—19	Yes Yes	Yes No	Good symptomatic relief, died with disseminated disease
H.A.	1½	W	M	Embryonal	Right orbit and nasal cavity	1	5	Irradiation	—	None	Right orbit, antrum, and nasopharynx	3.7 Pb—3,800—45	Yes	No	Died with disseminated disease
E.C.	9	N	F	Botryoid	Nasopharynx	3	3	Irradiation	—	None	Nasopharynx	3.7 Pb—4,300—34	Yes	No	Died rapidly with widely disseminated disease
J.J.L.	19	W	M	Alveolar	Left temple	1	12	Irradiation	—	None	Left temple	1 Cu—4,000—31 Radium—2,500 (implant) 3.7 Pb—3,800—17	Yes Yes	Yes No	Died with disseminated disease
R.J.	25	N	M	Alveolar	Right hand	2	8	Surgery	Irradiation	Cytosar-metacorten	Right forearm and hand	1 Cu—5,100—15	Yes	Yes	Developed necrosis, died of disseminated disease
W.S.	19	W	M	Embryonal	Left hand	4	10	Surgery	Irradiation	None	Left hand	1 Cu—4,000—23	Yes	No	Died with disseminated disease
D.G.	3	W	F	Embryonal	Right orbit	2	12	Surgery	Irradiation	Actinomycin D	Left orbit and antrum	3.7 Pb—4,000—29	Yes	No	Died with disseminated disease
S.D.	1½	W	F	Embryonal	Retropertitoneal	2	6	Surgery	Irradiation	Nitrogen mustard	Iliac lymph nodes Abdominal lymph nodes Left neck lymph nodes	3.7 Pb—2,100—14 3.7 Pb—2,620—37 2 Cu—2,160—10	No No No	No No No	Died with disseminated disease
D.H.	25	W	M	Embryonal	Right antrum	3	9	Irradiation	—	None	Right antrum	3.7 Pb—4,700—64	Minimal	No	Died of local extension no autopsy evidence of distant metastases
M.R.	4	W	F	Embryonal	Retropertitoneal	3	8	Surgery	Irradiation	Vinleukoblastin	Left upper quadrant of abdomen Left lower quadrant of abdomen Lung metastasis	9 Pb—5,000—44 9 Pb—5,150—36 9 Pb—2,000—15	Yes Yes Minimal	No Yes No	Died with disseminated disease
C.D.	4	W	F	Embryonal	Left ear	2	23	Surgery	Irradiation	Actinomycin D	Left supraclavicular and cervical lymph nodes	7 Pb—4,000—33 7 Pb—4,000—27 (Separated by 6 mo.)	Yes Yes	No Yes	Final local control achieved but patient developed contracted useless shoulder, died with disseminated disease

(1), and bladder-uterus-vagina (1). Pleural and peritoneal surfaces, particularly about the diaphragm, were the sites of metastases in 2 patients.

This widespread dissemination further confirms the impression of other authors that embryonal rhabdomyosarcoma is an aggressive, rapidly growing, and metastasizing neoplasm. That this metastatic tendency is not universal, however, is evidenced by the fact that 1 of our cases (D.H.), who presented with an embryonal primary tumor of the right antrum, died 9 months after external beam treatment, of local extension—with no evidence of metastatic spread on postmortem examination (Table x).

External beam therapy was employed almost exclusively. The quality varied with tumor site, from a half value layer of 1.02 mm. Cu to 9 mm. Pb. One patient (J. L.) with a left temporal primary lesion (alveolar type) received a tumor dose of 4,000 r in 31 days and the lesion was then implanted with radium for an additional tumor dose of 2,500 r. The involved left neck lymph nodes were treated to a tumor dose of 3,800 r in 17 days. Tumor ablation was achieved locally in the temporal fossa, but, despite the short interval of delivery and good initial regression, permanent control of the neck lymph nodes was not achieved and the patient died of disseminated metastases 12 months following treatment.

It is our feeling that, in general, one can seldom encompass the entire tumor with a radium implant (same inherent defect as a surgical approach) and we therefore prefer moderately large portal external beam therapy.

COMPLICATIONS OF RADIATION THERAPY

In 1 case (R.J.) a hand primary lesion was irradiated with a planned accelerated course (5,100 r tumor dose in 15 days) as a contemplated preoperative procedure. He subsequently developed evidence of disseminated disease and surgery was not performed. He died 8 months after irradiation with evidence of extensive local necrosis. In

another patient (C.D.) a primary lesion of the left ear was treated surgically, and the subsequently positive neck and supraclavicular lymph nodes on the left were treated with two courses of radiation therapy (4,000 r tumor dose in 33 days and 4,000 r tumor dose in 27 days) with an interval of 6 months between treatments. Local neck control was achieved but the patient developed contractural changes which resulted in a "frozen shoulder" and a useless arm. She died of disseminated disease 11 months after the original course of radiation therapy.

Three patients developed localized pulmonary fibrosis after treatment of metastatic lesions, but this was not, in itself, disabling in any patient. Small-portal convergent techniques were employed in the main, although one lesion was treated with a rotational technique.

During life, no clinical evidence of radiation nephritis was encountered, although 1 patient (M.R.) with a retroperitoneal primary lesion had evidence of marked unilateral radiation nephritis at autopsy (5,150 r tumor dose in 36 days).

RADIOTHERAPEUTIC TIME-DOSE "REGRESSION" OR "RESPONSE" AND LOCAL CONTROL OR TUMOR ABLATION

Our experience with embryonal rhabdomyosarcoma as pertains to survival figures in general parallels that of several reports in the literature. If, however, one wishes to assess the effectiveness or relative merits of one form of therapy compared to another (*i.e.*, irradiation and surgery), one must consider the local curative effectiveness of the modalities. The natural history of a tumor, of course, influences outcome and clinical prognosis, and, on occasion, choice of the primary therapeutic modality. We are concerned here in our radiotherapeutic techniques with two main factors—initial tumor regression (palliation) and tumor control (local ablation).

If the radiosensitivity of embryonal rhabdomyosarcoma were to be based on initial regression of tumor mass and relief of pain

TABLE XI
LOCAL RESULTS OF TREATMENT OF PRIMARY SITES IN 17 CASES

Treated	No. of Patients	Local Control	Significant Regression	No Significant Response
Head and Neck	9	3	8	1
Retroperitoneal	3	1	3	0
Extremity and Torso	3	2	3	0
Liver	2	0	1	1*
Total	17	6	15	2

* One treatment of 300 r tumor dose given and patient then placed solely on vincristine.

and associated symptomatology, then the responses of both the primary and secondary (metastatic) lesions treated in our series would indicate moderate sensitivity or radioresponsiveness. A significant response was noted initially in 15 of 17 cases of primary lesions and 8 of 12 cases of metastatic lesions (Tables XI and XII). If "moderate" doses were utilized (preferably 4,000 r tumor dose in 4 weeks), rather uniform regression and temporary response were obtained.

Permanent control, however, as evidenced by prolonged freedom from recurrence clinically, negative roentgen studies, and, more importantly, evidence of *local* tumor ablation on autopsied cases, required a significantly higher dose. Local tumor ablation or control was obtained in 6 of 17 patients in whom primary sites were irradiated (Table XI) and in 5 of 12 patients with metastatic foci (Table XII).

Time-dose responses are analyzed in Figures 8 to 10. In this series there were no

appreciable differences in the time-dose responses (for local ablation) between primary and metastatic lesions. The two cases which developed necrosis or significant complications are indicated by the keys to Figure 8 to 10. Tumor control or ablation could be obtained (not uniformly) with a tumor dose of 5,000 r in 5 weeks; however, more predictable tumor control required a tumor dose of about 6,000 r in 6 weeks.

The apparent responsiveness or sensitivity of the tumor, thus, initially is moderate, but local control or ablation requires a time-dose relationship in excess of 5,000 r tumor dose in 5 weeks, and preferably a tumor dose of 6,000 r in 6 weeks. In general, in the head and neck region, this can be administered, if one is willing to accept the sequelae of irradiation to adjacent more sensitive structures (*i.e.*, the eye). We do not, however, consider this a complication of head and neck irradiation for orbital and antral lesions, since it is a planned and ac-

TABLE XII
LOCAL RESULTS OF TREATMENT OF METASTATIC LESIONS IN 12 CASES

Site Treated	Control	No Control but Significant Response	No Significant Response	Total
Lung	3	0	1	4
Nodes	2	1	3	6
Soft tissue	0	1	0	1
Bone	0	1	0	1
Total	5	3	4	12

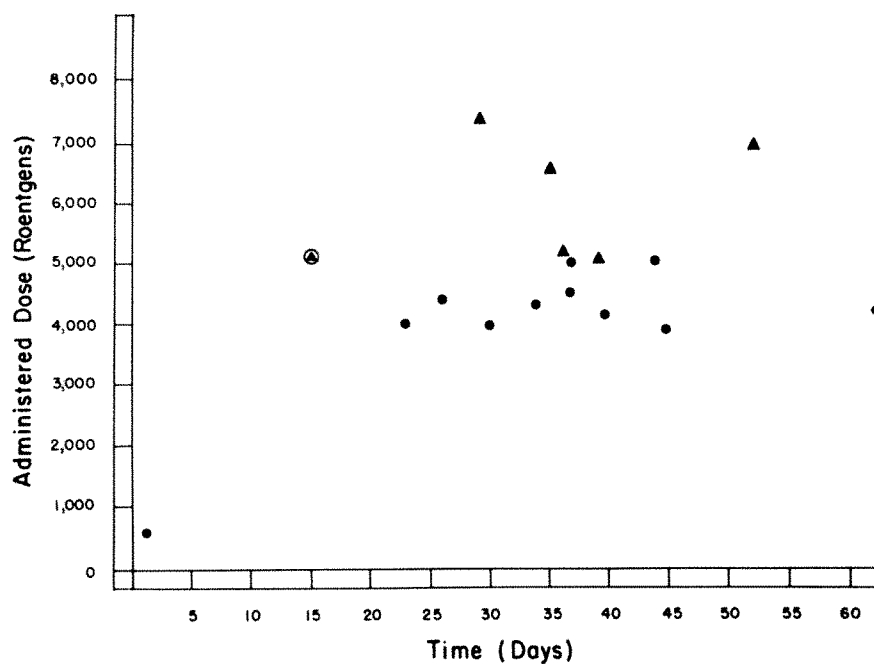


FIG. 8. Scatter diagram illustrating "time-dose" relationships of treatment plans in 17 primary sites and the therapeutic results. Closed circles represent failure of local control or ablation. Triangles represent treatment plans resulting in local "control." The ringed triangle represents a significant complication.

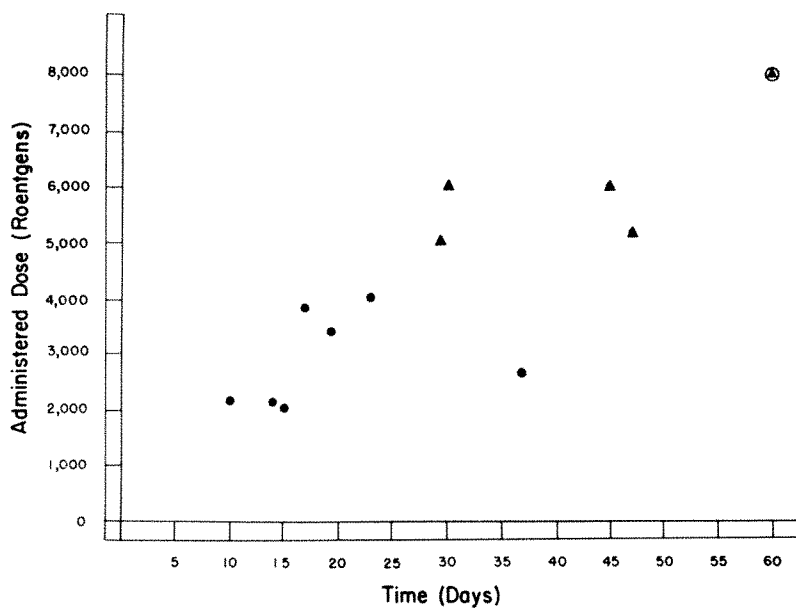


FIG. 9. Scatter diagram illustrating "time-dose" relationships of treatment plans in 12 metastatic sites and the therapeutic results. Closed circles represent failure of local control or ablation. Triangles represent treatment plans resulting in local "control." The ringed triangle represents a significant complication.

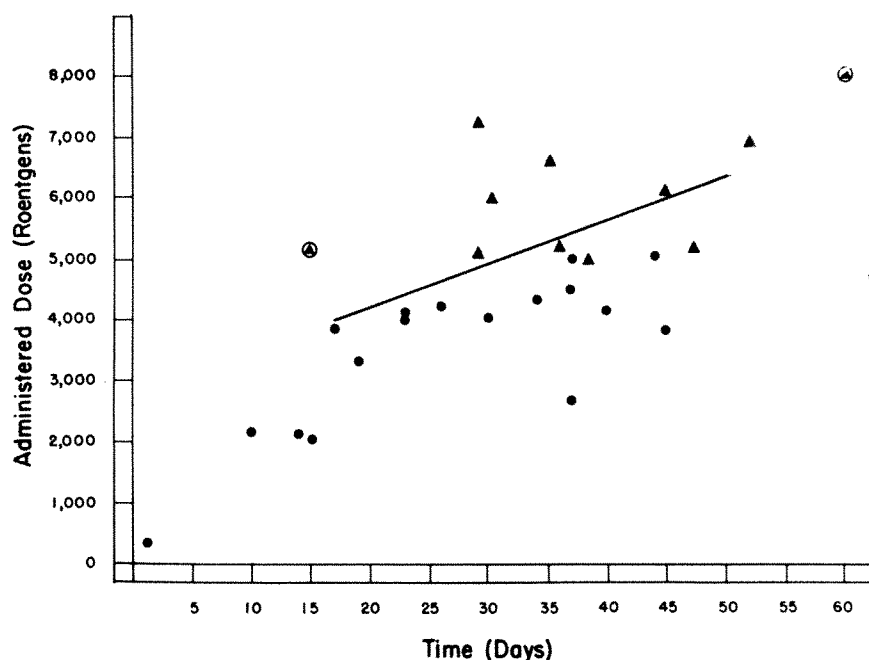


FIG. 10. Composite scatter diagram illustrating "time-dose" relationships of treatment plans in 29 sites (primary and metastatic combined) and the therapeutic results. Closed circles represent failure of local control or ablation. Triangles represent treatment plans resulting in local "control." The ringed triangles represent a significant complication.

cepted risk or price to pay for a local therapeutic "cure."

It is our feeling that, since these lesions do respond and can be controlled locally by "radical" irradiation, initial radical radiation therapy is the treatment of choice—especially in the head and neck region. This modality of primary therapy is also the choice of Moore and Grossi¹⁰ for primary lesions of the head and neck. This opinion is also based on the fact that most head and neck lesions as well as many girdle, torso, and retroperitoneal primary tumors do not usually lend themselves to complete surgical excision and extirpation. The more peripheral extremity lesions may be best treated by radical surgery (*i.e.*, amputation) if detected early and if there is no evidence of dissemination. The torso, girdle and retroperitoneal lesions are best treated by a combination of both radical surgery and irradiation. This combined approach deserves further evaluation as a planned procedure. The problems inherent in delivering a large-field exposure dose

greater than 4,000 to 5,000 r tumor dose can be readily appreciated when one is dealing with a liver or retroperitoneal primary lesion, especially with reference to the sensitivity of adjacent structures.

This implies a philosophy of treatment of maximal hope for the patient who does present with an apparently localized lesion, despite our present knowledge of the aggressive nature and early metastatic tendencies of this tumor.

It is our feeling that surgery, unless early and widely circumferential, does tend to disseminate the tumor even more rapidly, and therefore we do not advocate a "debulking" surgical procedure initially for primary lesions of the head and neck. Massive doses of radiation (7,000 to 8,000 r tumor dose) are not, in our experience, necessary for local control.

SUMMARY AND CONCLUSIONS

Twenty patients with embryonal rhabdomyosarcoma in a primary site other than the urogenital tract have been reviewed.

Twelve of our cases were children and 8 were adults. The histologic characteristics of the tumor types have been discussed. The anatomic location and histologic subtypes have been presented. Fourteen embryonal, 3 botryoid and 3 alveolar types in the following locations comprise our series: head and neck, 10 patients; liver, 2 patients; retroperitoneal, 3 patients; and extremity and torso, 5 patients. All of our retroperitoneal primary lesions occurred in females, and all extremity and torso primary lesions were in males, with the overall sex distribution showing a slight predominance of males. The intervals between the first symptom and pathologic diagnosis and between treatment and death in our failures were all quite short and only 6 patients are now alive. We have no long term survivals, although 3 patients are alive at $1\frac{1}{2}$, $2\frac{1}{2}$, and 3 years from definitive therapy, without evidence of disease. Three of our living cases had extremity lesions and only 1 survivor (3 years) had a head and neck primary lesion. The 2 surviving cases with liver primary lesions are not expected to represent "cures" or tumor control.

Analysis of treatment methods revealed the fact that the only survivor with head and neck involvement was treated by irradiation and chemotherapy. The other presently surviving patients (with extremity primary lesions) were treated surgically with reference to the primary tumor. Post-operative radiotherapy for residual local disease was required in 1 case, and metastatic sites were treated in the remaining cases. Apparently, early metastases are not widely disseminated in all cases, and the presence of a solitary pulmonary lesion should not necessarily preclude radical radiation therapy. Our 3 longest survivors ($1\frac{1}{2}$, $2\frac{1}{2}$, 3 years) all had an apparently successfully treated solitary lung lesion. That embryonal rhabdomyosarcoma initially is moderately responsive to radiation is evidenced by the significant regression noted in 15 of 17 cases with primary lesions and 8 of 12 patients with metastases. Local "control," however, was obtained in only 6 pri-

mary sites and 5 metastatic sites. Our series is not sufficiently large, in any anatomic area, to definitely establish radiation therapy as the modality of choice, but it should be pointed out that there is little information in the literature as to time-dose relationships with reference to the treatment of embryonal rhabdomyosarcoma. It is our feeling that in the past insufficient dosage has been employed in a so-called "curative" attempt locally (*i.e.*, a tumor dose of 4,000 r or less in 4 weeks), resulting in regression without permanent local control.

The response to chemotherapy was, in general, disappointing, although in 1 patient a significant response to actinomycin D and in 2 striking responses to vincristine were obtained. Further evaluation of vincristine and vinca compounds is probably indicated to establish the efficacy of this agent, either palliatively or in combination with the other definitive modalities, in the treatment of the soft tissue sarcomas.

Our experience with embryonal rhabdomyosarcoma would indicate that it is not, in fact, a very radiosensitive tumor, but that it can be controlled or ablated locally with a relatively high degree of assurance, provided a proper time-dose relationship is maintained (*i.e.*, a tumor dose of 6,000 r in 6 weeks). The decision to initially employ radical radiation therapy will, of course, depend upon the clinical extent of disease when the patient presents for treatment.

Analysis of our series indicates that, in general, radical radiation therapy is the treatment of choice for the initial apparently localized primary tumor (except perhaps for extremity locations). However, the natural history of the tumor and usual clinical course, as manifested by a rapid growth rate and relatively early widespread metastases, is followed all too frequently by failure of all attempts at therapy.

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LIFE HISTORY OF MELANOMA*

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TWO cutaneous lesions—nevi and melanoma—are inevitably related in medical thinking either because of the likelihood of evolution of the benign into its malignant counterpart or because of the frequent difficulty in differentiating the two lesions, one from the other.

Pack *et al.*¹⁴ have noted that the average white individual harbors at least 14.6 nevi of one type or another. It was Allen and Spitz,¹ however, who pointed to the significance of the junctional change and made the observation that the junctional or compound nevus occurs most frequently on the hands, feet and genital areas.

In 100 unselected individuals examined by Allyn *et al.*³ the over-all incidence of nevi on the palms and soles was 14.3. The darker the skin, the greater was the incidence of nevi in this series. Usually, there was only one lesion per anatomic site. Palmar distribution was fairly uniform, whereas on the soles there was a distinct concentration along the longitudinal arch. Pack, Lenson and Gerber¹⁴ failed, just as did Allyn *et al.*,³ to observe a single instance of subungual nevus in 1,632 examinees. Several authors have described a variable sex incidence, but the declining incidence of nevi with advancing years is generally recognized. In a series of patients with melanoma at Memorial Hospital, there was a distinct concentration of lesions on weight bearing points.

Much interest has centered around Lancaster and Nelson's⁹ study of the incidence of moles and melanoma in red and fair haired persons exposed to excessive sunlight. Pack *et al.*¹⁴ are in agreement with this point of view. They have noted the high racial incidence of nevi in white persons

(14.6 per person) as compared with that in Negroes (2 per person).

Several facts arise from epidemiologic studies of the relationship of moles and melanoma. Subungual nevi are very rarely observed; melanoma in this anatomic site is not uncommon. Nevi are rare on the soles of Negroes' feet while melanomas are not infrequently observed there. The greatest number of moles on the feet are not located along the weight bearing points as are melanomas.

There is no question that the incidence of melanoma among dark skinned races in many other countries compares with that observed among white people in the United States and fair haired Nordics.

FAMILIAL ASPECTS

That hereditary factors bear a definite relationship to melanoma in animal life has been documented by Gordon⁶ and others. The influence of heredity on human melanoma was first described by Cawley⁷ and later substantiated by Miller and Pack¹³ and others. Schoch's¹⁵ observation of a mother and her 2 adult sons, all of whom were found to have melanoma at ages of 60, 18, and 35, respectively, led to cytogenetic studies of the chromosomes and other cellular elements. He concluded that the hereditary defect in his cases lay with the genes at a "subchromosomal level."

POSSIBLE ENDOCRINAL RELATIONSHIPS

Nevi are commonly observed in children, young adults and people in mid-life but are less frequently seen in those of advancing years. Though true melanoma does occur in children with extreme rarity, the incidence of metastasizing melanoma begins to take

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on real significance after puberty, increasing with each decade up to the age of 50, thereafter declining moderately but significantly. Primary melanoma of the vulva and vagina most commonly occurs in females over 60 years of age. The incidence of melanoma is greater among females than males; however, this may be the result of a selective process due to their greater interest in health measures and personal appearance. Certainly, females with melanoma are younger than males in most stages of the disease.

The influence of pregnancy is a highly controversial though moot point. Almost all clinicians familiar with the problem have observed a number of pregnant females in whom a congenital mole, or one of long standing, has taken on great growth activity, including metastasis. Though this observation is one which never fails to impress the clinician, there is no question that many of these same females had undergone a previous pregnancy without demonstrable growth activity in the same mole. George, Fortner, and Pack⁵ have shown that an untoward influence of pregnancy will not bear statistical evaluation. In a comparison of 115 women, 16 to 43 years old, who became pregnant during the course of this disease with 141 nongravid females of similar age, there was no greater incidence of growth activity. On the other hand the group of pregnant females with melanoma had the higher incidence of regional lymphatic metastasis. The 5 and 10 year survival rate, cancer free, was the same for both groups. Though the statistical data do not favor such a relationship, we do not believe that the subject is closed.

DURATION OF MOLE

Melanoma may be of two types, congenital or *de novo* (Fig. 1 and 2). At varying periods after the onset of puberty, a previously brown mole may start to grow, become darker in color or simply cause itching. This may occur at ages 15, 50, or 70. Such congenital-type moles should always be excised surgically and examined histo-



FIG. 1. Congenital type of melanoma demonstrating central clearing or possibly spontaneous healing.

logically. The *de novo* type of melanoma occurs prior to puberty with extreme rarity. Not too infrequently, however, the history may be of several years' duration. In other instances, the growth may be of very recent onset and possess capacities for rapid growth and metastasis.

Appearance of a metastasis prior to awareness of the presence of the primary melanoma. At times, the presence of an enlarged lymph node in one of the accessible areas may be the first warning of melanoma, once lymphoma has been excluded. An exact

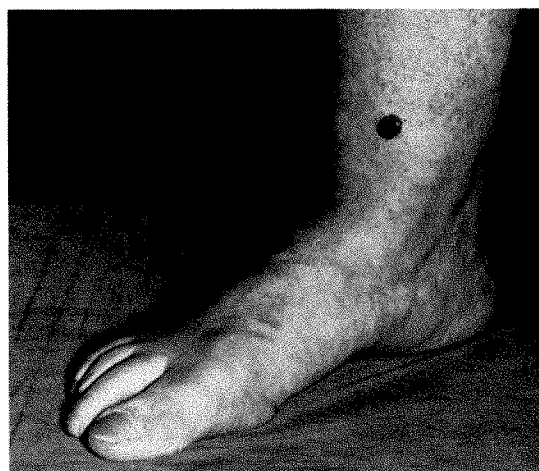


FIG. 2. *De novo* type of melanoma of skin of right leg.

diagnosis requires surgical excision and histologic interpretation of the lymph node.

DIAGNOSIS OF MALIGNANT MELANOMA

The differential diagnosis concerned in the management of the case suspected of representing malignant melanoma most frequently includes the following lesions: (a) benign pigmented nevus, (b) Jadassohn's nevus, (c) pigmented basal cell epithelioma, (d) Kaposi's disease, (e) pigmented seborrheic keratosis, (f) hemangioma, (g) hematoma, (h) freckles, and (i) juvenile melanoma.

Surgical excision and histologic examination are the only means of determining the exact diagnosis.

UNKNOWN PRIMARY ORIGIN

Not too infrequently the clinician is asked to see a patient with an enlarged lymph node in one of the accessible or regional chains. The patient gives no history of previous treatment of a mole; none is visible on the body surface or within the orifices. The clinical diagnosis may suggest lymphoma. A diagnosis of metastatic melanoma is rendered by the pathologist and, yet, a thorough examination of the patient does not disclose the source of the metastasis. This occurred in 37, or 3.7 per cent, of 992 patients at Memorial Hospital,⁴ of whom 13 had Stage III malignant melanomas and were hopelessly incurable. Of 24 patients in Stage II, 10 were cancer free at 5 years after radical surgical treatment. This observation strongly supports the concept of treating cancer where it is seen, if clinically it appears to be curable. The rationale for the occurrence of this apparent phenomenon is not entirely clear. Nevertheless, neither nevi nor melanomas arise primarily in the lymph nodes. Many clinicians of experience have observed partial regression in melanomas, particularly those of the congenital type. It is not illogical to suppose that in these few cases spontaneous regression has been complete, especially in those who are apparently cured.

BIOPSY TECHNIQUE

To perform a biopsy, with but rare exceptions, the entire mole and several millimeters of surrounding skin and underlying fat should be excised. Unless unusually expert pathologic consultation is available, the frozen section technique is not recommended. Erroneous interpretation of frozen section material may produce more serious consequences than the few days' delay required to obtain paraffin sections.

If the melanoma is ulcerated or fungating, wedge removal of a specimen may be performed.

LYMPHATIC SPREAD

In order to determine a logical approach to the problem of dissection of the regional lymph nodes, the charts of all patients with melanoma of the trunk and extremities at Memorial Hospital were reviewed. These charts contained both clinical and autopsy material data. The incidence of lymphatic metastasis was recorded for melanoma from every anatomic site and the results were tabulated. It was, therefore, possible to predict with reasonable accuracy the lymphatic drainage area which would be involved with metastatic cancer in each individual case.

PREDICTABLE LYMPHATIC SPREAD IN MALIGNANT MELANOMA

MELANOMA OF THE UPPER EXTREMITY

1. Contrary to some opinions, subungual melanomas were found to metastasize to the lymph nodes of the ipsilateral axilla as frequently as primary lesions of the hand, finger and forearm (about 30 to 39 per cent of cases). Hence, routine radical dissection of the axillary lymph nodes would appear to be indicated in all instances of melanoma originating in the subungual region, the fingers, hand, forearm and arm.

2. Melanomas occurring in the skin of the shoulder should be considered separately from the standpoint of potential and actual metastasis to lymph nodes. In 8 out of 10 cases of melanoma of the anterior shoulder, the presence of metastasis was

histologically established in the ipsilateral neck lymph nodes; consequently, it is our belief that in all such cases a routine radical neck dissection is indicated. In 60 per cent of the cases of primary melanoma of the posterior shoulder, metastases were found in the lymph nodes of the ipsilateral axilla. We, therefore, feel that in these cases a radical dissection of the axillary lymph nodes should be performed.

3. Metastasis to the lymph nodes of the epitrochlear area was so infrequently observed in patients with melanoma of the hand and forearm that routine dissection of this area does not seem to be indicated.

MELANOMA OF THE TRUNK

1. Since there is a direct communication between the lymphatics of the infraclavicular region and the cervical lymph nodes, it is our opinion that a radical neck dissection should be considered in all cases of melanoma of the infraclavicular region.

2. The lymphatics from midline locations, either anteriorly or posteriorly, drain bilaterally to the lymph nodes of the axilla or groin, depending upon the anatomic level of the midline lesion. Hence, bilateral dissection of the axillary or groin lymph nodes should be carried out as indicated.

3. In melanoma of the lateral trunk, a definite zone of demarcation, defining the direction of lymphatic spread appears to lie at the level of the 8th rib; *i.e.*, below this level, lymphatic drainage is primarily toward the ipsilateral groin, whereas melanoma above this line generally metastasizes to the ipsilateral axilla. In our experience, melanoma of the lateral trunk was not noted to metastasize to the contralateral lymph node bearing area. The appropriate management of the lymph nodes, therefore, would depend on the relationship of the primary site to the 8th rib.

4. Melanoma of the suprapubic area metastasized bilaterally to the lymph nodes of the groin in the few cases observed in this series. This, we feel, suggests that a radical dissection of both groins should be performed for melanoma so encountered.

MELANOMA OF THE LOWER EXTREMITY

Metastasis to the lymph nodes of the ipsilateral groin is invariably the first lymph node involvement from melanoma arising from any given anatomic site on the lower extremity.

Metastasis to the popliteal lymph nodes is so rare that the possibility of its occurrence should not enter into the concept of management of melanoma of the lower extremity inferior to the condyles. Interpretation of our data implies the need for routine, radical groin dissection in all patients with melanoma originating in the skin of the lower extremity.

SURGICAL TREATMENT

PRIMARY TUMOR

The primary tumor is best managed by wide excision with or without skin grafting under general rather than local anesthesia. A skin ellipse is made surrounding the lesion at a distance of at least 5 cm., lateral to the tumor on either side in the horizontal plane. The center or tumor bearing portion of the ellipse is placed eccentrically and distally for the reason that local metastasis and/or recurrence usually appears proximal to the primary site.

MANAGEMENT OF THE REGIONAL LYMPH NODES

Surgical removal of the primary tumor may be accomplished by excisional techniques; however, the success or failure of the entire management program depends on the treatment of the regional lymph nodes.

The clinical stage of the disease, the location of the primary lesion, our knowledge of the anticipated lymphatic spread from the various anatomic sites, the factors which may lead to local metastasis and/or recurrence are all matters of concern in the individual patient.

SURGICAL TREATMENT ACCORDING TO STAGE OF MELANOMA

Stage I and II. When the disease is clinically confined to the primary site (Stage I), controversy exists in regard to the manage-

ment of the regional lymph nodes. Our study shows that in nearly 25.0 per cent of 335 instances of clinically negative lymph nodes, metastatic melanoma was actually present histologically in the surgical specimen. Furthermore, the 5 year survival rate, cancer free, was 53.0 per cent in these patients as opposed to 10.0 per cent for those in whom the lymph nodes were clinically positive for cancer. Hence, it is felt that dissection of clinically negative lymph nodes will lead to a much greater opportunity for clinical cure for those who are found to have cryptic lymphatic metastases.

As a result of our clinical and autopsy studies, we believe that, for all practical purposes, the popliteal and epitrochlear lymph nodes do not share in the lymphatic spread of malignant melanoma. Hence, we will describe as regional, the cervical, axillary and inguino-femoral lymph nodes.

The concept of resecting the primary site simultaneously in continuity with the regional lymph nodes is just as basic in the management of malignant melanoma as in all other varieties of cancer, since 50 per cent of Stage I melanomas will metastasize to lymph nodes within 10 months of initial treatment of the primary lesion.

The timing of the lymphatic dissection would seem to present a problem only when one or more major joints separate the point of origin from the regional lymphatics. Ideally, the optimum time for lymphatic dissection is at the first operative seance as far as the convenience of the patient and the earliest possible phase of the disease are concerned. Nevertheless, many objections to this concept have been raised for apparently sound reasons. The danger of intervening metastasis or local recurrence is cited as the most logical and valid argument against simultaneous but dissepate excision of the primary lesion and the regional lymphatics. Our investigations have shown that intervening metastasis and/or local recurrence occurs in a fairly high percentage of cases (15-30 per cent), no matter when the lymphatic dissection is performed. This phenomenon was observed most often

when numerous metastases were encountered in the dissected lymph nodes and only rarely in those cases where the lymph nodes were clinically negative. Because of the high 5 year cancer free survival rate in these patients, we feel that simultaneous dissection of the regional lymph nodes, even when the procedure cannot be carried out in one continuous surgical field, should be performed.

The capacity of malignant melanoma to recur or metastasize locally after seemingly adequate surgery is well known (Fig. 3). It is possible, however, that in transit metastasis may have occurred in microscopic form prior to excisional treatment of the primary lesion, only to appear beyond the margins of the excision later on. This may explain the appearance of such lesions after both limited and extensive excisional measures. Furthermore, not infrequently metastatic or "satellite" lesions are observed proximal to the primary lesion before any treatment whatsoever has been initiated. In general, such isolated or even sparsely scattered metastases are proximal to the tumor, indicating that spread has occurred via the lymphatics.

Method of treatment and its relation to



FIG. 3. Local recurrence.

local metastasis and/or recurrence. Of 468 patients who were operated on for melanoma in Stages I and II, there were 76 (16.3 per cent) who subsequently developed locally recurrent manifestations of the same disease (Table I). Mention has already been made of the tendency for this to occur after local excisional measures (10.0 per cent), but the appearance of such lesions in 7 of 46 patients (15.2 per cent) who underwent major amputation is tragic indeed. It is after dissection of the regional lymphatics, however, that this tendency for locally recurrent manifestations is most apparent (55 of 278 dissections, or 19.8 per cent), especially when the site of the primary lesion and the regional lymphatics are separated by one or more major joints. If treatment of the primary lesion and the lymph nodes has been simultaneously but disseparately performed, the recurrence rate may be as high as 37.2 per cent. This is undoubtedly the reason why monobloc or in continuity procedures are advocated wherever possible. Nevertheless, even under these circumstances, the local recurrence rate is 11.3 per cent.

Local metastasis and/or recurrence in relation to status of lymph nodes. The most striking feature where local recurrence was manifest was observed to be in regard to the status of the regional lymph nodes. In over 80 per cent of cases of local recurrence, the lymph nodes contained clinically evident and histologically established evidence of metastatic melanoma. This factor

then would seem most responsible for the production of local recurrence by mechanically blocking the lymphatic pathway from the primary site to the drainage basin. This seems to be especially pertinent after our review of a series of 78 patients in whom the lymph nodes were clinically negative but histologically positive. In this group the local recurrence rate was 18.0 per cent. Since the 5 year cancer free survival rate was so high in this group (52.6 per cent), elective, simultaneous, disseparate dissection would seem warranted.

The selection of a mode of treatment is not made easy by the complications of this disease. In 27.5 per cent of our cases the recurrence was so disseminated that no surgical technique could encompass all the lesions. In others, amputation was performed in order to remove all visible disease. Where locally recurring melanoma could be completely removed by excisional and dissection procedures, the results obtained were found to be comparable with those in which amputation was performed.

Amputation. The therapeutic role of major amputation or exarticulation has not as yet become clearly defined. It is our opinion, however, that the simultaneous presence of the primary lesion and regional lymph nodes in the absence of distant metastasis is an indication for amputation.

Hemipelvectomy. In Miller's¹² series of 13 patients who submitted to hemipelvectomy for recurrent and metastatic melanoma, there were no 5 year survivors. The experi-

TABLE I
LOCAL METASTASIS AND/OR RECURRENCE OF THE EXTREMITIES
OCCURRING SUBSEQUENT TO FIRST DEFINITIVE TREATMENT

	No. of Operations	No. of Recurrences/Metastases	Per Cent
All Operations	468	76	16.3
Excisions	144	14	10.0
Dissections	278	55	19.8
Disseparate simultaneous	43	16	37.2
Disseparate subsequent	120	26	21.7
Monobloc	115	13	11.3
Amputations	46	7	15.2

ence of McPeak, McNeer, Whitely and Booher¹¹ was similar. It may be said, therefore, that any patient found to have metastatic melanoma above the inguinal ligament will not benefit from this operation.

RADIATION THERAPY

Hillriegel⁸ reported a series of 259 malignant melanomas in which roentgen therapy was employed. His reported 5 year survival rate for Stage I was 62 per cent and for Stage II 23 per cent. Not all primary lesions or lymphatic metastases were biopsied; nevertheless, his illustrations showed regression of both primary and metastatic melanoma in some cases. He advocates intensive preoperative irradiation followed by local excision in 6 to 8 weeks. Hilaris *et al.*⁷ have reported clinical improvement in patients submitted to palliative roentgen therapy for metastatic malignant melanoma in bone and brain.

PERFUSION OF THE EXTREMITIES

After more than 4 years' trial of whole limb perfusion with phenylalanine mustard, Stehlin *et al.*¹⁶ observed striking responses in many primary lesions and intermediate metastases. Whether the method will serve to prevent local recurrence or enhance the outlook of the potentially curable patient remains to be seen. These authors emphasize the experimental nature and the hazards of the procedure.

END RESULTS

Eight hundred and four patients with histologically established melanoma of the trunk and extremities were observed between the years 1935 and 1955, thus affording survival data over a period of 20 years (Fig. 4).

Since our main interest is concerned with the results of the surgical treatment of patients with potentially curable melanomas, we will discuss only the cases found to have melanoma localized to the original site (Stage I) or to have demonstrable metastasis in one regional lymphatic drainage area (Stage II). All patients received surgical treatment and are accounted for in tabular form.¹⁰

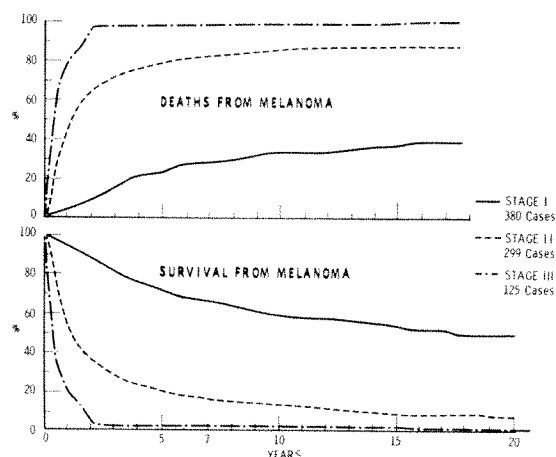


FIG. 4. Actuarial curves showing death and survival rates in all 3 clinical stages of melanoma. (Reproduced with permission from *Surgery*.)

Stage I. Five year survival was obtained in 71 per cent of 359 patients in Stage I (Fig. 5). Because a significant number die of cancer after attaining an apparent cure, we believe that a more definitive period lies somewhere between 7 and 10 years post-operatively, when the survival rate was 65 and 62 per cent, respectively. After 10 years the patient is presumably cured, though an occasional instance of late metastasis will occur.

Stage II. In this stage, the profound effect

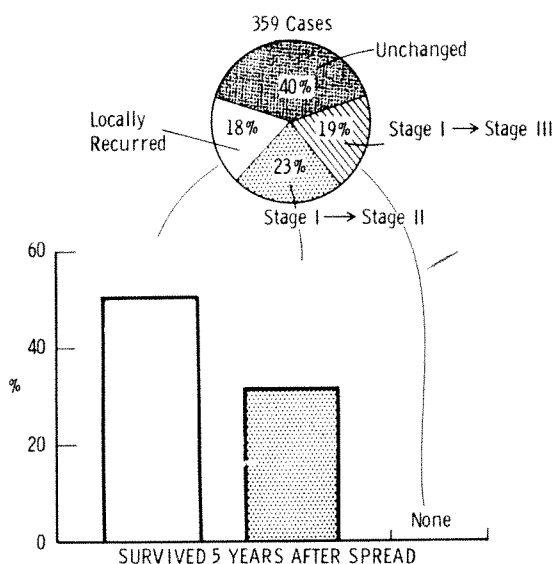


FIG. 5. Behavior of Stage I melanoma. (Reproduced with permission from *Surgery*.)

of the metastasis to the regional lymph nodes on prognosis was noted. At the 5 year period only 19 per cent of the patients were cancer free, at 7 years and 10 years 17 and 12 per cent, respectively, were alive.

SUBSEQUENT HISTORY OF PATIENTS WITH MELANOMA IN STAGE I

In 40 per cent of the patients there will be no further manifestation of the disease (Fig. 5). If the regional lymph nodes are managed by periodic observation and removed only when clinically significant rather than as part of the first surgical effort, metastasis (Stage I→Stage II) will occur in 23 per cent. The 5 year survival rate in these patients will be 30 per cent. Eighteen per cent will recur locally and it is anticipated that 50 per cent of these patients will remain cancer free at 5 years. Finally, it is significant that 19 per cent in this favorable group of cases will develop distant metastasis without regional metastasis (Stage I→Stage III) and will die of cancer.

FACTORS WHICH MAY INFLUENCE THE OUTCOME

Sex. The factor of greater concern for personal appearance and health is probably the more important factor behind the 73 per cent 5 year survival in females as opposed to 65 per cent for males.

Age. The more youthful subjects have an excellent prognosis, for in this group of Stage I patients 5 year survival occurred in 82-86 per cent of cases up to age 40 as compared to 48 per cent after age 70.

Longevity of the mole. Although anticipating a more favorable outlook for patients with congenital moles or with moles of long duration, there was no significant difference in the end results as compared with the *de novo* variety.

Histologic features of the primary lesion. It is difficult to relate the histologic features of the primary tumor to prognosis. Nevertheless, it has been observed that melanomas less than 1 cm. in diameter, demonstrating minimal dermal invasion

and external elevation above the skin, offer a better outlook for 5 year survival than large proliferating, ulcerating and deeply invasive neoplasms.

DEATHS FROM MELANOMA

An analysis of the deaths from melanoma according to stage is given in Figure 4.

Stage I. While 24 per cent of patients in Stage I die of melanoma within the first 5 years, 34 per cent will have died at 10 years. Careful scrutiny of Stage I curve in Figure 4 indicates that between 7 and 10 years postoperatively a patient may be considered as cured of melanoma. Subsequent recurrence is unusually rare.

Stage II. While 84 per cent of Stage II patients will have died from melanoma within 10 years, subsequent recurrence is so unusual that patients who are cancer free at 10 years can be regarded as cures (Stage II curve in Fig. 4).

Stage III. Ninety-nine per cent of Stage III patients will have died of cancer within 1 year after the first clinical evaluation. An occasional patient will survive who demonstrates metastasis to more than one lymphatic area or to distant organs in solitary fashion (Stage III curve in Fig. 4).

EXTENT OF METASTASES AT NECROPSY

At necropsy of patients dying with melanoma, metastasis is found in nearly every organ of the body. Whereas the frequency of metastases to the lung and liver is well known, the really common involvement of the stomach (26 per cent); small intestine (58 per cent); colon (22 per cent); pancreas (53 per cent); bone (30-40 per cent); brain (39 per cent) and heart (49 per cent) is not so generally realized (Fig. 6). Finally, nearly all the lymphatic drainage basins are diffusely involved by metastasis.

CONCLUSIONS

Benign nevi and malignant melanoma are observed in people of all races and nationalities. Melanoma occurs most com-

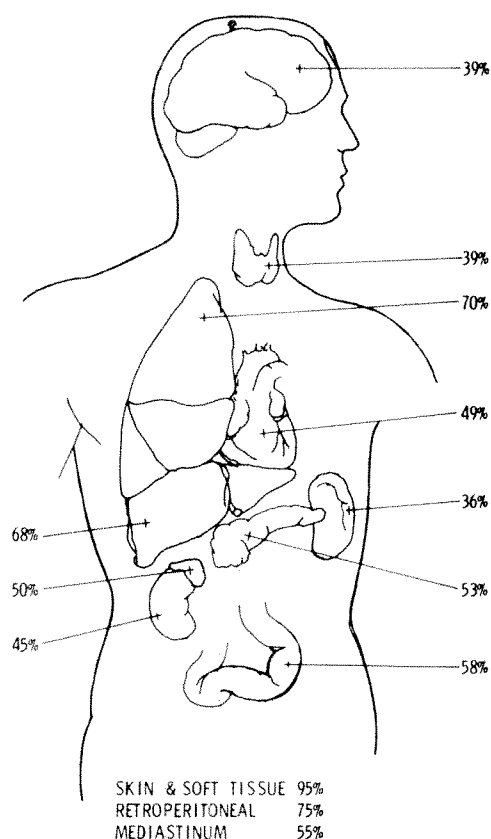


FIG. 6. Major incidence of metastasis as found at necropsy.

monly in the third to the fifth decades of life.

Melanoma metastatic to lymph nodes in the absence of a known primary lesion suggests the possibility of an origin from a spontaneously healed primary.

With radical treatment of the primary tumor and regional lymph nodes, long term survival may be anticipated in the majority of the Stage I patients.

Postmortem examination demonstrates that melanoma has the capacity to metastasize to all the organs of the body.

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TUMOR SIMULATING INTRATHORACIC EXTRAMEDULLARY HEMOPOIESIS*

CLINICAL AND ROENTGENOLOGIC CONSIDERATIONS

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BONE marrow heterotopia in the form of tumor simulating masses is a compensatory phenomenon encountered in conditions associated with abnormal hemopoiesis. For many years the process has been recognized in postmortem histologic sections. However, recently several cases of marrow heterotopia in the thorax were diagnosed by chest roentgenography.^{1,4,5}

The author reported elsewhere⁶ that development of bone marrow heterotopia in the thorax follows a constant anatomic pattern, resulting in a typical roentgen appearance; *i.e.*, ovoid or round, well outlined soft tissue densities, usually multiple, located posteriorly, adjacent to the thoracic spine and presenting lobulation or a segmental arrangement. These masses are asymptomatic and their roentgenologic recognition is of value in the differential diagnosis of tumors of the posterior mediastinum.

Recently, several new cases have been observed which, although giving further support to the above described roentgenologic picture, have presented additional clinical and roentgenologic findings, necessitating a reevaluation of the subject. The clinical material on which this report is based consists of 5 patients of Greek origin with Mediterranean anemia who demonstrated tumor simulating intrathoracic extramedullary hemopoiesis.

REPORT OF CASES

CASE 1. B.C., a man aged 24 years, was admitted to our department because of recurrent ulcers of both ankles. A diagnosis of Cooley's anemia had been made at the age of 12 years.

On examination the patient was pale, had muddy yellow skin, and appeared younger than

his age. He had mongoloid facies with prominent cheek bones, flat frontal bones, and an arched hard palate. The liver was slightly enlarged. There was general enlargement of the lymph nodes, particularly in the axillae. Chronic ulcers were present in the region of the ankles.

The hemoglobin was 8.7 gm./100 ml.; hematocrit 27 per cent; red blood cell count 3,520,000, with anisocytosis, poikilocytosis, microcytosis, target cells, hypochromia, and anisochromia. There were 7,150 white blood cells per cu. mm., with 60 per cent polymorphonuclears, 36 per cent lymphocytes, 3 per cent eosinophils, and 1 per cent monocytes. There were 9 erythroblasts per 100 white blood cells in the peripheral blood. The serum bilirubin was 0.9 mg./100 ml. direct, and 0.48 mg./100 ml. indirect. The bone marrow showed marked hyperplasia of the red blood cell series, the white blood cell series, and many megakaryocytes. There was no abnormality in the maturation of the red blood cells. The serum albumin electrophoresis pattern showed a moderate increase in the gamma globulin. The hemoglobin electrophoresis pattern revealed 90 per cent hemoglobin 'F'. The sickle-cell preparation test was negative. Studies with radioactive chromium 51 revealed that the life span of the red blood cells was 17 days for Cr⁵¹ T_{1/2} (normal range 27 to 36 days); the surface count was 2,429 counts/min. over the spleen and 2,701 counts/min. over the liver, with a ratio of 0.89 (normal ratio 1.0). The red blood cell radioactive iron 59 uptake was 18 per cent in 10 days (normal range 85 to 100 per cent). The iron plasma clearance was 20 minutes for Fe⁵⁹ T_{1/2} (normal range 60 to 120 minutes). The surface count revealed no increase in the radioactivity over the liver or spleen but a high degree of ineffective hemopoiesis of the bone marrow. The findings indicated Cooley's anemia.

A roentgenologic bone survey showed changes

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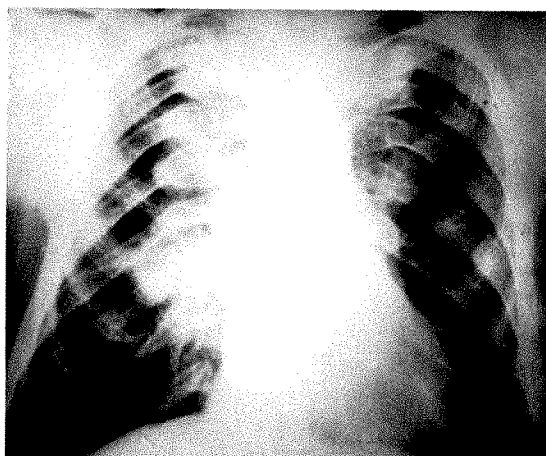


FIG. 1. Case 1. Posteroanterior roentgenogram of the chest showing multiple bilateral masses.

compatible with thalassemia. A roentgenogram and a laminagram of the chest showed soft, well-defined, lobulated masses measuring from 2 to 6 cm. in diameter, lying posteriorly in the paravertebral gutter from D2 to D10 (Fig. 1 and 2). The possibility of intrathoracic extramedullary hemopoiesis was considered.

Needle aspiration of the masses, through the right fifth intercostal space paravertebrally under fluoroscopic control, revealed elements usually found in the bone marrow (Fig. 3, *A* and *B*). The material obtained was rich in cell elements and precursors of red blood cell series and in granulocytic white blood cells. Occasional plasma cells and reticulocytes were present. The red blood cells were more numerous than the white blood cells (200 red blood cells per 100 white blood cells) with a significant percentage of proerythroblasts and basophilic erythroblasts (9 per cent and 39 per cent, respectively) and no megakaryocytes.

Satisfactory healing of the tibial ulcers and some improvement in the hematologic appearance was noted during the patient's stay in the hospital.

CASE II. B.F., a man aged 21 years, entered the hospital because of marked anemia, which had been diagnosed at the age of 6 years as Cooley's anemia.

Physical examination revealed mongoloid facies and swelling of the abdomen due to splenomegaly and, to a lesser degree, hepatomegaly. Ulcerations of the skin of the feet were present.

Hematologic studies showed changes com-

patible with hemolytic anemia: hemoglobin 8.5 gm./100 ml.; hematocrit 28 per cent; red blood cell count 3,520,000, with anisocytosis, poikilocytosis, microcytosis, hypochromia, target cells, and basophilia; the white blood cells numbered 43,000 per cu. mm., with 69 per cent polymorphonuclears, 19 per cent lymphocytes, 10 per cent monocytes, and 2 per cent eosinophils. The serum iron was 121.5 γ /100 ml. and blood bilirubin 1.3 mg./100 ml. The hemoglobin electrophoresis pattern showed a large amount of hemoglobin 'F'. The bone marrow showed marked hyperplasia, especially of the red blood cell series. The Cr^{51} test revealed a red blood cell life span of 14 days for $\text{Cr}^{51} \text{T}_{1/2}$. The iron clearance was 17 minutes for $\text{Fe}^{59} \text{T}_{1/2}$. The red blood cell Fe^{59} uptake was 13.5 per cent in 10 days. The relative surface count rate over the sacral bone revealed ineffective hemopoiesis.

Roentgen examination of the bones showed changes compatible with Cooley's anemia. A chest roentgenogram of the patient showed small masses in the right paraspinal area, measuring 1 to 2 cm. (Fig. 4).

During his stay in the hospital, the patient was given blood transfusions and other suppor-

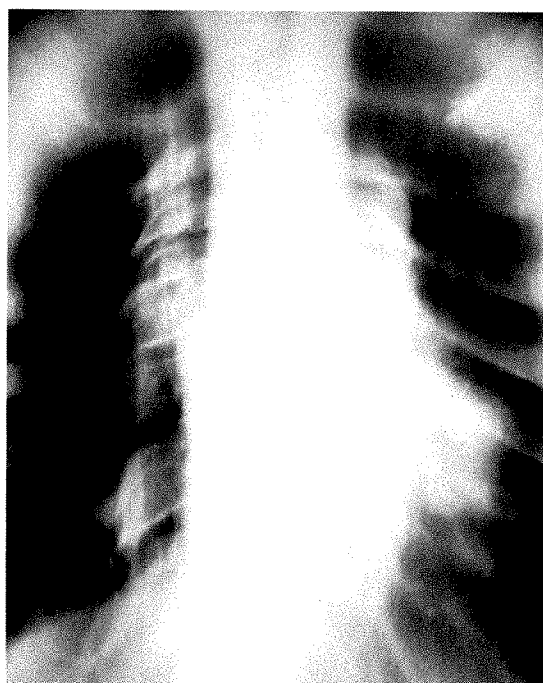


FIG. 2. Case 1. Laminagram of the chest showing the segmental arrangement of the masses.

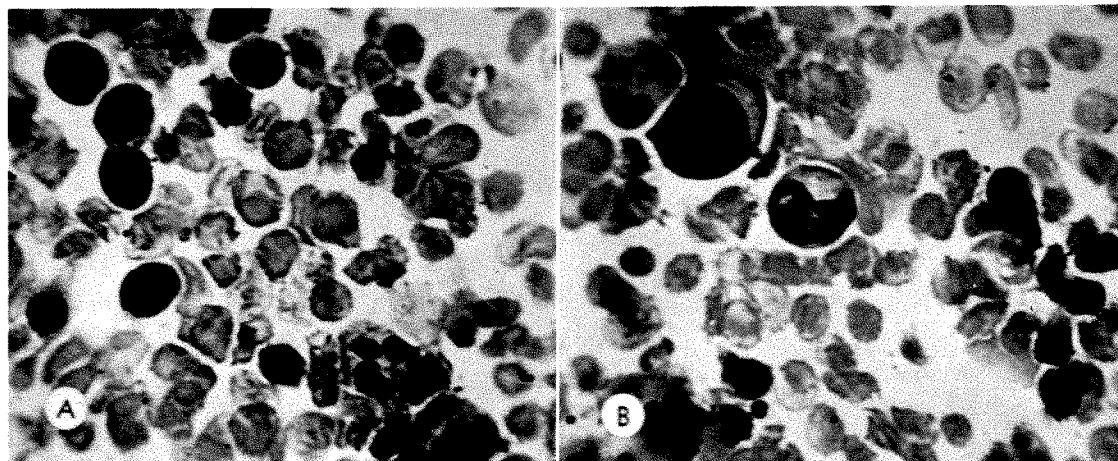


FIG. 3. Case 1. (A and B) Microphotographs of material obtained by needle aspiration. Erythroblasts and leukoblasts of different maturation are seen.

tive therapy. He was discharged and asked to return for follow-up examinations.

CASE III. P.L., a man aged 28 years, entered the hospital for an annual check-up for Cooley's anemia.

Hematologic studies revealed a microcytic hypochromic anemia, with marked morphologic alterations of the peripheral red blood cells. Hemoglobin was 7.4 gm./100 ml.; hematocrit 23 per cent; red blood cell count 2,990,000, with anisocytosis, poikilocytosis, microcytosis, and macrocytosis; there were

3,500 white blood cells per cu. mm., with 51 per cent polymorphonuclears, 44 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophils. The serum iron was 117 γ /100 ml. and the serum bilirubin 1.75 mg./100 ml. A bone marrow puncture showed increased hyperplasia of all cell series. The Cr^{51} test revealed a red blood cell life span of 21 days for $\text{Cr}^{51} \text{ T}_{1/2}$. The iron clearance was 20 minutes for $\text{Fe}^{59} \text{ T}_{1/2}$. The red blood cell Fe^{59} uptake was 19 per cent in 10 days. The surface count rate over the sacral bone marrow revealed ineffective erythropoiesis as usually seen in Cooley's anemia.

Roentgen examination of the bones revealed changes typical of Cooley's anemia. A chest roentgenogram showed 2 ovoid masses, partially superimposed on the right side above the diaphragm, and a third on the left side (Fig. 5).

A splenectomy was advised and the patient was referred to the surgical department.

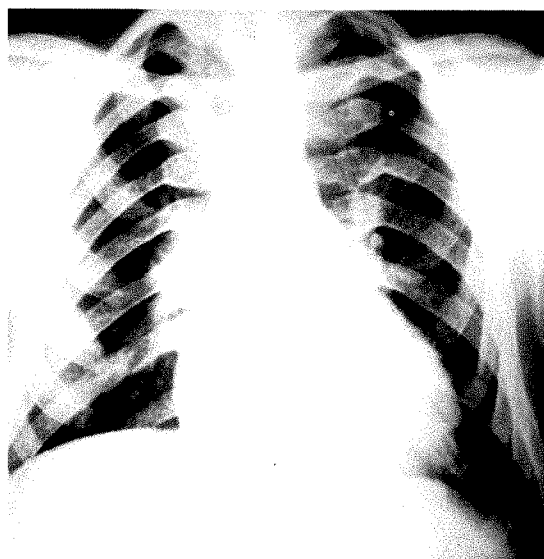


FIG. 4. Case II. Nodules in the right paraspinal area.

CASE IV. H.D., a girl aged 14 years, was admitted to the hospital for "paraplegia of lower extremities." Cooley's anemia had been diagnosed at an early age and splenectomy was performed at the age of 4. Six months before admission the patient developed muscular weakness of both lower extremities which progressed steadily to paralysis and inability to walk.

Physical examination revealed mongoloid facies, muddy yellow skin and hepatomegaly. Hematologic studies showed a hemoglobin of 8.6 gm./100 ml.; a red blood cell count of 3,350,000, with anisocytosis, microcytosis and

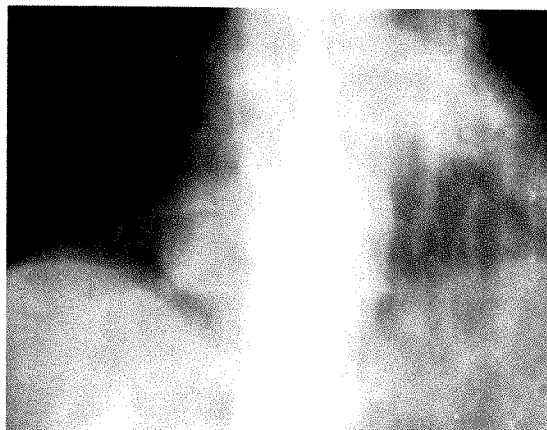


FIG. 5. Case III. Bilateral masses above the diaphragm.

hypochromia; hematocrit was 30 per cent; white blood cell count 14,000, with 34 per cent polymorphonuclears, 46 per cent lymphocytes, 10 per cent monocytes, 7 per cent eosinophils and 3 per cent basophils. The serum iron was 270 γ /100 ml. and blood bilirubin 1.20 mg./100 ml. The cerebrospinal fluid protein was 1.20 mg./100 ml.

Neurologic examination showed pyramidal tract signs from the lower extremities: hypesthesia from T₄-T₅ and below, and muscular atrophy of the lower extremities. The impression was "transverse myelopathy due to lesion at T₄-T₅." A myelogram was made which revealed a complete block at the same level.

Chest roentgenograms (Fig. 6 and 7) and a laminagram (Fig. 8) demonstrated a round,

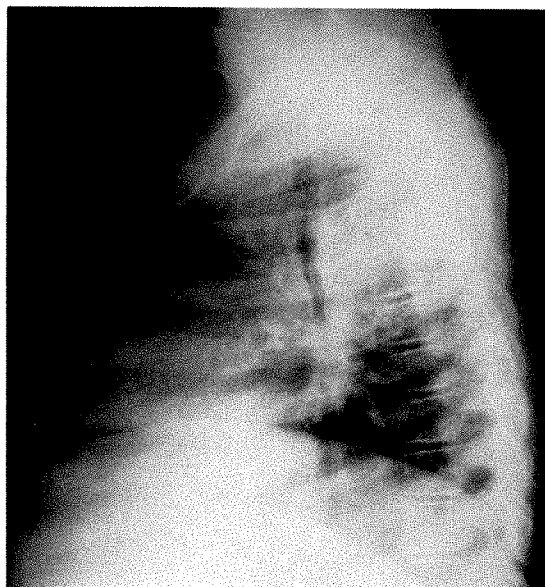


FIG. 7. Case IV. In the lateral roentgenogram the mass is seen posteriorly, compressing slightly the wall of the trachea.

4 cm. in diameter, mass located in the right costovertebral angle adjacent to T₄ and T₅ which was described as typical of heterotopic marrow. A scintiscan of the chest after injection of 250 μ c of Au¹⁹⁸ showed good correlation with the heterotopic marrow at the right paraspinal area (Fig. 9).

The neurologic findings were attributed to pressure from this mass and radiation therapy was instituted. Using a cobalt 60 teletherapy unit, 900 rads were delivered to the mass in 9 days by a posterior port. The patient showed

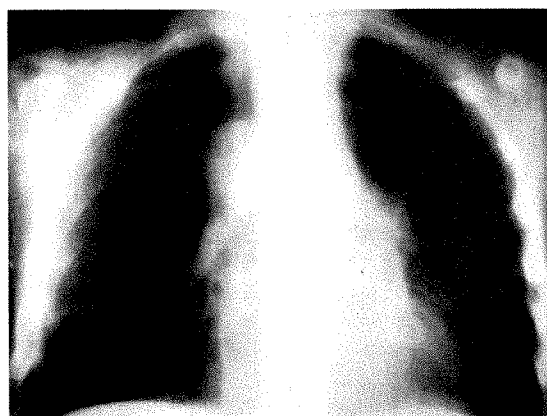


FIG. 6. Case IV. Posteroanterior roentgenogram of the chest showing a mass in the right paraspinal area.

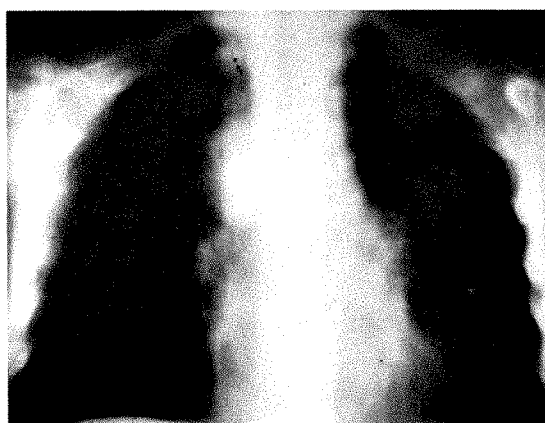


FIG. 8. Case IV. Laminagram (at 7 cm.) showing the mass.

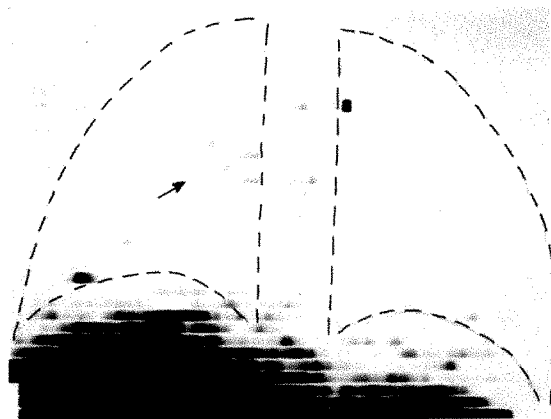


FIG. 9. Case IV. Photoscan after injection of Au^{198} showing good correlation with roentgenographic findings.

striking improvement of both sensory and motor neurologic symptoms.

CASE V. H.F., a male aged 32 years, had Cooley's anemia since an early age. A brother and sister of the patient also had the same disease.

Physical examination revealed dark yellow skin, mongoloid facies and hepatosplenomegaly.

Blood examination showed a red blood cell count of 1,910,000 per cu. mm., reticulocytes 0.2 per cent, hematocrit 14 per cent, hemoglobin 4.8 gm./100 ml., and a normal number of platelets. The white blood cell count was 3,400, with 54 per cent polymorphonuclears, 40 per

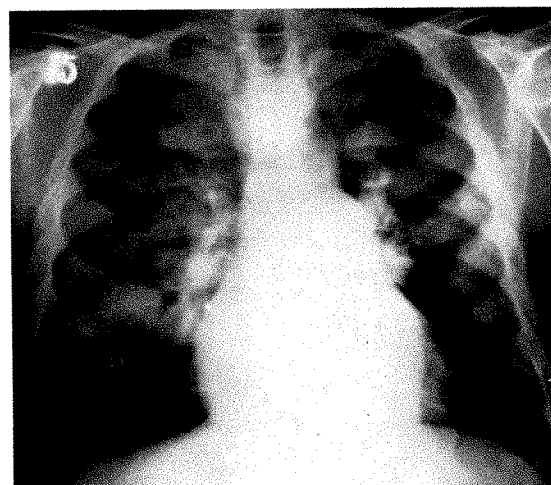


FIG. 10. Case V. Posteroanterior roentgenogram of the chest showing multiple bilateral masses.



FIG. 11. Case V. In the lateral roentgenogram the masses are located well posteriorly.

cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, and 1 per cent basophils. There were 2 erythroblasts per 100 leukocytes. Liver function tests: ZnSO_4 14.7 u; thymol turbidity 14.7 u; and cephaline cholesterol flocculation test + + + +. Total protein 7.3 gm./100 ml.; albumin 3.5 gm., globulin 3.8 gm., and ratio 0.92. The alkaline phosphatase was 6.2 King-Armstrong units, uric acid 5.3 mg./100 ml., blood urea 0.64 gm./100 ml., and glucose 1 gm./100 ml. A marrow puncture revealed findings compatible with follic acid deprivation.

An electrocardiogram showed right axis deviation and premature auricular contractions.

Bone survey demonstrated osteoporosis and trabeculation of bones, typical of Cooley's anemia. Chest roentgenograms (Fig. 10 and 11) and a laminagram (Fig. 12) showed multiple masses partially superimposed, appearing as a single density with lobulated borders. Transverse laminagrams (Fig. 13 and 14) revealed the location of the masses to be in the posterior mediastinum. Two smaller masses, 2 to 3 cm. in diameter and ovoid, were attached to the anterior part of the 5th and 6th rib (Fig. 15).

During his stay in the hospital, the patient received follic acid, blood transfusions and other

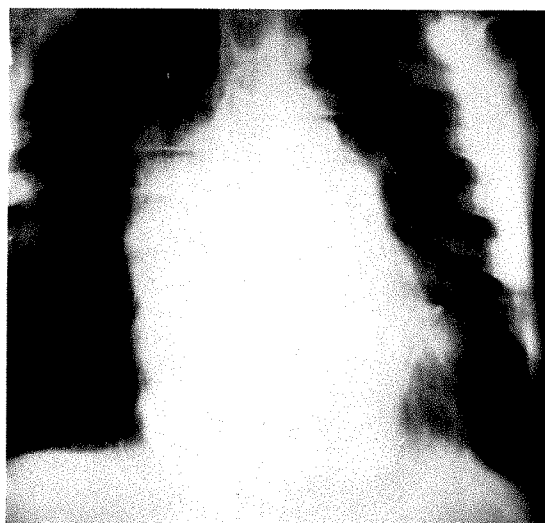


FIG. 12. Case v. Laminagram (at 6 cm.) showing the masses as a single density with lobulated margins.

supportive therapy, resulting in improvement of the hematologic condition.

CLINICAL CONSIDERATIONS

Tumor simulating bone marrow heterotopia is not an uncommon phenomenon, although usually an incidental finding on chest roentgenograms of patients with Cooley's anemia. Of 45 patients admitted to our hospital with thalassemia, 5 presented

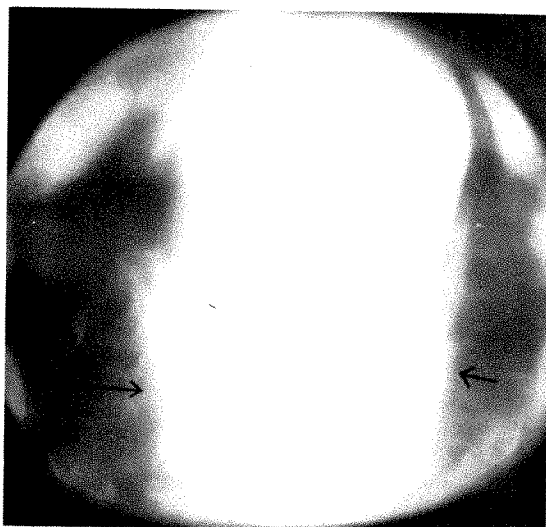


FIG. 13. Case v. Transverse laminagram at the level of D10 showing the masses (more prominent in the left) to be located in the posterior mediastinum.



FIG. 14. Case v. Transverse laminagram at the level of D4 showing the masses in the costovertebral angle.

intrathoracic marrow heterotopia in the form of masses, an incidence of 11 per cent. The process is observed mainly in patients with severe long standing anemia. All 5 patients had hepatosplenomegaly, multiple bone changes, mongoloid facies and other usual clinical features and laboratory findings of advanced Cooley's disease. We felt that the roentgenologic recognition of these masses is of value in ruling out other entities, usually neoplastic, located in the posterior mediastinum. Indeed, Knebel reports a case of bone marrow heterotopia.

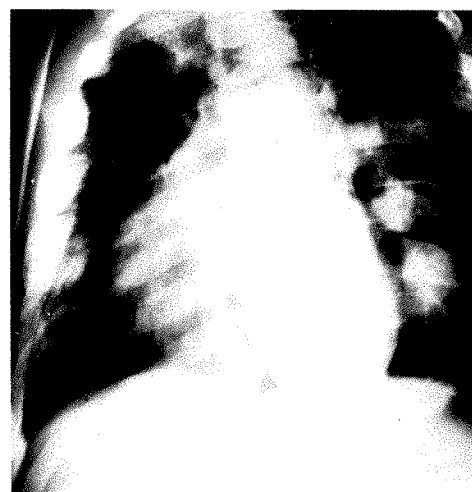


FIG. 15. Case v. Oblique chest roentgenogram showing a small mass "attached" to the anterior aspect of the sixth rib.

in a patient who underwent an unnecessary thoracotomy for a "neurogenic tumor of the posterior mediastinum." Histologic examination of the excised mass showed heterotopic bone marrow and the patient, in retrospect, was found to have thalassemia minor. If one is aware of this entity, the nature of the masses can be easily recognized, especially in association with the history of anemia, the clinical picture and the other laboratory findings.

Although masses of heterotopic bone marrow are usually asymptomatic, in 1 of our patients, they were associated with symptoms due to pressure on adjacent organs, *i.e.*, the thoracic portion of the spinal cord. The patient presented paraplegia with sensory disturbances. All neurologic signs disappeared after a course of radiation therapy, in which 900 rads were delivered to the mass in a period of 9 days. To the best of our knowledge, this is the only case reported of masses of heterotopic bone marrow causing pressure symptoms. Irvine and Robertson² recently described a similar case of spinal cord compression caused by heterotopic bone marrow; however, they do not mention roentgenologic evidence of intrathoracic masses.

ROENTGENOLOGIC FINDINGS

The tumor-like masses of heterotopic bone marrow are located mainly in the posterior mediastinum and particularly in the costovertebral angle. This is well demonstrated in lateral chest roentgenograms where the masses are clearly visualized. In laminagrams they appear only in the posterior sections of the chest (Fig. 2, 8, and 12). Figures 13 and 14 demonstrate the masses in transverse laminagrams, their symmetric bilateral location in the costovertebral angle being evident. Most often, they are multiple, of soft tissue density with well-defined margins and presenting symmetric segmental arrangement (Fig. 1 and 4). When, however, superimposition occurs, they appear as a single density with lobulated borders (Fig. 12). In addition, in Case v, smaller ovoid masses, 2 to 3 cm. in

diameter, were seen adjacent to the anterior part of the 5th and 6th ribs bilaterally (Fig. 15). This part and the corresponding posterior part of the ribs usually undergo the greatest expansion and trabeculation. In retrospect, a similar appearance, although less prominent, was noted in Case 1. These 2 cases were the most advanced ones. Since these masses were attached to the most expanded, osteoporosed and trabeculated portions of the ribs, one may assume that they originated from the marrow of the adjacent bone of the vertebral body or rib; *i.e.*, the marrow, after it "overflowed" the bone, spread around it. This hypothesis based only on roentgenologic evidence is contradictory to the autopsy findings reported by Ask-Upmark,¹ who found in his case no connection between the masses and the marrow of the adjacent bone.

In general, intrathoracic extramedullary hemopoiesis takes the form of masses located in the costovertebral angle. However, sometimes in advanced cases, additional masses of heterotopic marrow develop adjacent to the anterior part of the ribs. Table 1 gives the roentgenographic findings in detail.

It is of interest that the mass in Case iv was demonstrated on a scintiscan of the thorax after intravenous injection of colloidal Au¹⁹⁸. Kniseley *et al.*³ were able to demonstrate the distribution of hemopoietic bone marrow with satisfactory detail by scintiscanning, thereby exploiting the observation that the distribution of intravenously injected colloidal gold in the bone marrow correlates well with the areas of active hemopoiesis. In this patient, we used a similar technique and we found an excellent correlation between the roentgenographic and scintiscanning findings.

SUMMARY

1. Of 45 patients with Cooley's anemia, 5 presented masses of intrathoracic extramedullary hemopoiesis, an incidence of 11 per cent.

TABLE I

Case	Red Blood Cell Count	Hemoglobin	Chest Roentgen Findings
I	3,520,000	8.7 gm.	Multiple bilateral masses, 2-6 cm., presenting segmental arrangement in the posterior mediastinum Small mass (2 cm.) attached to the anterior part of the fourth rib on the left
II	3,520,000	8.5 gm.	Small masses presenting segmental arrangement in the right upper mediastinum, 2 cm. in diameter
III	2,990,000	7.4 gm.	Two masses 4-5 cm. in diameter in the right posterior mediastinum partially superimposed, one in the left
IV	3,350,000	8.6 gm.	Single density 4 cm. in diameter in the right posterior mediastinum
V	1,910,000	4.8 gm.	Large multiple bilateral masses in the posterior mediastinum, superimposed, appearing as a single density with lobulated borders Masses 2-3 cm. in diameter "attached" to the anterior part of the fifth and sixth ribs bilaterally

2. The location and development of these masses follow a constant anatomic pattern, resulting in a typical roentgenographic appearance. They represent, therefore, a separate roentgenologic entity.

3. This entity should be included in the differential diagnosis of tumors of the posterior mediastinum, particularly in patients with long standing anemia.

4. Although the process is usually asymptomatic, in 1 of our patients it was associated with symptoms due to pressure on the spinal cord.

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INTRAPELVIC DOSE DISTRIBUTIONS FROM A DOUBLE CROSSARM RADIUM APPLICATOR*

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A NUMBER of different designs have been advocated for rigidly constructed uterocervical radium applicators, each of which represents the experience and personal ideas of some specialist in the field. Several such devices, usually identified by the names of their originators, are now being produced commercially with varying degrees of acceptance. While these individual models may differ considerably in appearance and mechanical complexity, their essential features are generally similar: one or more pairs of ovoids, laterally spaced to occupy the vaginal fornices, and attached at right angles to a cylindrical uterine tandem of two or three removable sections. The whole assembly serves primarily as a framework to hold the multiple radium sources in fixed geometric relation to each other, and to the anatomic areas under treatment, so that predictable and reproducible dose patterns may be delivered.

Unfortunately, the usual methods of calculating dosage from such applicators are not only laborious, but are subject to some quite appreciable errors due to variations in absorption by the supporting metal structures. In originally computing the standard "linear source tables"^{2,3,4} which now constitute our basic reference data for such work, careful provisions were made to incorporate adequate correction factors for attenuation in the different effective thicknesses of material which are introduced by different angles of radiation emergence, both through the platinum container and within the radium salt itself. In dealing with the single, isolated, and uniformly cylindrical shapes postulated by these tables, therefore, no significant errors are to be expected providing the specified dis-

tances can be accurately determined. When several such sources are distributed through a three dimensional structure of cross braced metallic tubing, however, the problem becomes considerably more complicated.

Since the nominal wall thickness of most of the commercially manufactured metal applicators is between 1.5 and 2.0 mm. of brass (or stainless steel or monel), our usual procedure with this type has been to add all the individually evaluated contributions from each of the radium sources to obtain the total dose at a given point, and then to subtract an average correction factor of approximately 9 per cent for absorption by the additional metal. It is apparent, however, that this method can compensate adequately for only that fraction of the radiation which happens to emerge at a nearly perpendicular angle through a single wall of the assumed thickness.

A theoretically more accurate approach is available through use of the recently revised linear source tables of Greenfield *et al.*,³ which have been extended to include values for 1.0 mm. platinum filtration. If the usual 0.5 mm. Pt tube or needle is loaded into one of the cylindrical 1.5 to 2.0 mm. brass walled compartments of an applicator, the total effective absorption by the two concentric envelopes may be considered approximately equivalent to that of 1.0 mm. Pt.² The tabular data for that thickness will then provide dosage figures which are specifically compensated for exit angles of the radiation, if only a single cylindrical section of the applicator is considered at a time. It is obvious, however, that due to the mutual shadowing effects of the several active sections and their irregularly shaped supporting members,

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there will still be major local departures from the calculated dose distribution, which are not amenable to correction by any simple formula.

Ernst¹ has solved these particular problems, in the case of his own design of expanding metal applicator, by compiling charts of directly measured doses to supersede any such relatively uncertain theoretical calculations. Using a specially designed small scintillation probe, he recorded the actual dose rates in roentgens per hour at each 1 cm. interval on each of two 10×10 cm. coordinate grids, which correspond respectively to the lateral and anteroposterior pelvic planes. In addition to the composite dose distribution patterns produced by a number of different recommended loading combinations, there is appended a set of tables which specify the individual contribution from a single radium source in any one of the nine compartments of the applicator, to any point in either of the two reference planes. By means of these tables, any possible combination of sources which can be placed within the Ernst applicator may be quickly evaluated. Due at least in part to the availability of such conveniently pre-recorded dosimetric data, Ernst's device has become a favored modality for much of the routine uterocervical work in this department.

As with any such standardized apparatus, however, circumstances contraindicating its application do arise. In a considerable number of cases, the vaginal fornices are found to be too narrow to permit correct expansion of the lateral arms, even after removal of the outermost pair of ovoids. Since use of the dose distribution charts is valid only under exactly duplicated conditions of full extension, that major advantage is then entirely lost. Under these conditions, it is our practice to employ the smaller and simpler (and less expensive) device designated in the Radium Chemical Company's catalog as a "double crossarm applicator three section tandem," but referred to by some as a "cross-tee." Since this applicator is used so frequently

and since our radiotherapists have become so accustomed to the convenience of the Ernst tables, it was determined to prepare corresponding data for the cross-tee technique.

Although specially designed measuring apparatus had to be built for Ernst's original work, we were more fortunate in having at hand a commercially produced instrument to serve the same purpose. The Curtis Nuclear Company's "Probitron" features a scintillator crystal in the tip of a slender stainless steel probe, intended for insertion into body cavities. The associated photomultiplier and amplifier circuits are amenable to calibration directly in roentgens per hour, by reference to a standard radium source, and show adequate short-term stability for this purpose. The only part of our equipment which required special construction was the measuring phantom, shown in Figure 1. This is a waterproof lucite box, 30 cm. square \times 15 cm. deep. The 2.5 cm. thick bottom of the box is recessed to hold a cross-tee applicator horizontally, in either anteroposterior or lateral aspect. A pattern of holes is drilled through the box top and part way into the bottom, so that when the probe is inserted through one of the top

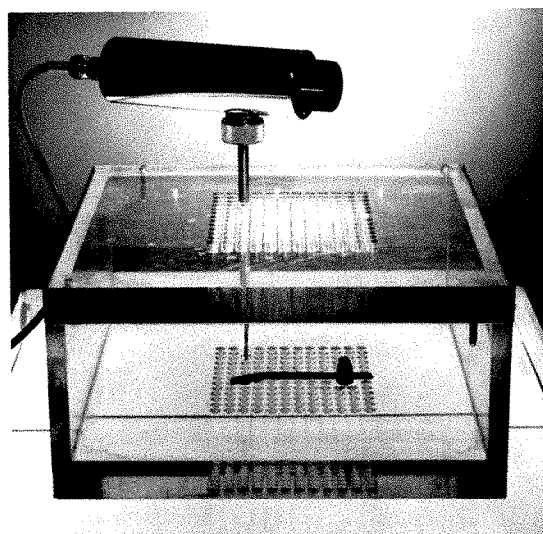


FIG. 1. Water-filled lucite phantom with applicator and scintillation probe in position for radiation measurements.

	RIGHT					LATERAL PELVIC FIELDS						LEFT				
	6	5	4	3	2	1	2	3	4	5	6					
A	6.9	8.9	12.1	16.4	29.0	I	29.0	16.4	12.1	8.9	6.9					
B	7.9	10.9	15.9	23.9	68.0		68.0	23.9	15.9	10.9	7.9					
C	8.9	12.7	18.5	28.2	71.8		71.8	28.2	18.5	12.7	8.9					
D	10.3	14.0	20.5	30.5	54.6		54.6	30.5	20.5	14.0	10.3					
E	11.3	15.7	23.2	36.8	75.2	II	75.2	36.8	23.2	15.7	11.3					
F	12.0	16.8	25.5	41.3	85.8		85.8	41.3	25.5	16.8	12.0					
G	^B 12.3	17.7	27.6	^A 46.3	86.2		86.2	^A 46.3	27.6	17.7	^B 12.3					
H	12.0	18.1	29.6	52.1	113.9	III	113.9	52.1	29.6	18.1	12.0					
I	11.7	17.4	29.8	62.2			62.2	29.8	17.4	11.7						
J	10.6	15.8	26.8	54.5	IV	V	54.5	26.8	15.8	10.6						

FIG. 2. Total dose rate measurements, in roentgens per hour, for lateral pelvic fields. Uniform loading density of 10 mg. radium with 0.5 mm. platinum filtration in each compartment of applicator. Coordinate grid lines spaced 1.0 cm. apart.

holes, the center of the crystal at its distal end is accurately supported at a corresponding point in the mid-plane of the applicator. These index holes, spaced 1.0 cm. center to center, define the coordinate grid of measurement points shown in Figures 2 and 3. When the box is filled with water and placed on a stack of Masonite boards, it forms an "infinite" phantom for measurements under full tissue equivalent backscatter conditions.

Since we followed Ernst's original idea and since his system of reference coordinates and tabular arrangement of data is both familiar and convenient, our own measurements are presented as nearly as practicable in the same format.

Since the cross-tee applicator has only 5 compartments instead of the 9 found in Ernst's version, and since there would be little advantage gained by any laterally

asymmetric loading of the 2 rather closely spaced ovoids (IV and V of Figure 2), the quantity of data to be recorded in this case is appreciably lessened. We have also omitted graphic dosage charts for all except the representative conditions of uniform distribution,* using 10 mg. of radium with 0.5 mm. Pt filtration in every compartment. Figure 2 shows the total dose received in each square centimeter of the bilaterally symmetric pelvic plane when such uniform loading is used. Figure 3 does the same for the anterior (bladder) and posterior (rectal) fields, which differ somewhat from each other due to the anteriorly directed bend of tandem section I.

For any other possible distribution of radium in this applicator, the doses delivered to any of the points in the lateral fields of Figure 2 may be obtained from Table 1. Doses to any of the points in the

	BLADDER				PELVIC FIELDS						RECTAL	
	6	5	4	3	2	1	2	3	4	5	6	
K	7.1	9.7	13.7	20.4	I	39.0	24.7	15.7	11.1	8.2	6.3	
L	8.3	12.1	19.3	34.5		43.6	21.3	14.0	10.1	7.3		
M	9.5	13.4	21.1	37.0		47.7	25.3	16.4	11.4	8.4		
N	10.5	14.5	21.8	34.1	55.8	II	46.5	28.9	18.8	13.0	9.5	
O	11.0	15.8	23.5	37.7	76.3		72.8	34.6	21.5	14.6	10.2	
P	11.5	16.4	25.0	41.1	86.8		83.3	39.5	23.8	15.5	10.9	
Q	11.5	16.8	26.4	44.2	85.0	III	83.5	42.9	25.1	16.2	11.1	
R	11.2	16.5	26.6	45.1	97.8		96.7	44.4	25.5	16.0	10.8	
S	10.5	15.3	25.0	43.1	IV & V		43.4	24.1	15.0	10.1		
T	9.5	13.7	21.7	36.3		35.7	20.8	13.3	9.1			

FIG. 3. Total dose rate measurements, in roentgens per hour, for anterior (bladder) and posterior (rectal) pelvic fields. Uniform loading density of 10 mg. radium with 0.5 mm. platinum filtration in each compartment of applicator. Coordinate grid lines spaced 1.0 cm. apart.

anterior and posterior fields of Figure 3 may be found from Tables II and III, respectively. Since each compartment will accept sources up to a maximum of 4 mm. diameter \times 21 mm. length, a considerable range of choice is available. Whenever any loading other than 10 mg. is to be used in a particular compartment, it is only necessary to multiply the dose contribution listed for that compartment by a factor $S/10$, where S is the actual strength in milligrams of the radium source chosen. As a practical example, suppose the following loading is preferred: 30 mg. in I, 10 mg. in II, zero in III, and 20 mg. each in IV and V. If we wish now, for instance, to determine the dose to "point B" (coordinates 6 G, Table I), we multiply the value 1.7 from column I by $30/10$ to obtain the corrected

value 5.1 r/hour. Similarly, 2.9 from column II, times $10/10$, equals 2.9; 3.0 from column III, times zero, equals zero; 3.1 from column IV, times $20/10$, equals 6.2; and 1.6 from column V, times $20/10$, equals 3.2. The total dose at this particular point is then $5.1 + 2.9 + 0.0 + 6.2 + 3.2 = 17.4$ r/hour, instead of the 12.3 r/hour total which is shown in the table for uniform loading with 10 mg. in each compartment.

All data presented herewith are for radium needles or tubes having a filtration of 0.5 mm. of platinum or its equivalent.² Since the same kind of oblique absorption errors discussed above might be re-introduced if an attempt were made to substitute other thicknesses with blanket correction factors, it is considered more desirable to limit the choice of radium sources to this

TABLE I
RIGHT LATERAL PELVIC FIELD

Pelvic Position	Radium (10 mg.) Loading						Pelvic Position	Radium (10 mg.) Loading					
	I	II	III	IV	V	Total		I	II	III	IV	V	Total
2A	23.5	2.8	1.0	1.0	0.7	29.0	6E	2.8	3.1	2.3	1.9	1.2	11.3
3A	10.9	2.8	1.0	1.0	0.7	16.4	2F	5.5	53.4	16.4	6.5	4.0	85.8
4A	7.0	2.4	1.1	0.9	0.7	12.1	3F	4.7	17.3	10.4	5.7	3.2	41.3
5A	4.3	2.0	1.0	0.9	0.7	8.9	4F	3.6	8.5	6.3	4.5	2.6	25.5
6A	2.9	1.6	1.0	0.8	0.6	6.9	5F	2.8	4.9	4.0	3.3	1.8	16.8
2B	59.5	4.9	1.4	1.3	0.9	68.0	6F	2.4	3.1	2.7	2.5	1.3	12.0
3B	15.9	4.3	1.6	1.2	0.9	23.9	2G	3.3	22.9	41.3	11.8	6.9	86.2
4B	8.8	3.5	1.5	1.2	0.9	15.9	(A) 3G	3.0	12.0	16.2	10.3	4.8	46.3
5B	4.9	2.7	1.4	1.1	0.8	10.9	4G	2.5	7.1	8.0	6.9	3.1	27.6
6B	3.1	1.9	1.2	1.0	0.7	7.9	5G	2.0	4.2	4.7	4.6	2.2	17.7
2C	56.8	9.8	2.3	1.8	1.1	71.8	(B) 6G	1.7	2.9	3.0	3.1	1.6	12.3
3C	15.9	7.2	2.3	1.7	1.1	28.2	2H	2.1	10.0	58.9	31.2	11.7	113.9
4C	8.6	5.1	2.1	1.6	1.1	18.5	3H	2.1	7.5	17.5	18.6	6.4	52.1
5C	5.0	3.4	1.8	1.5	1.0	12.7	4H	1.9	5.1	8.5	10.4	3.7	29.6
6C	3.1	2.3	1.5	1.1	0.9	8.9	5H	1.5	3.5	4.9	6.0	2.2	18.1
2D	23.9	22.5	3.9	2.6	1.7	54.6	6H	1.3	2.4	3.1	3.7	1.5	12.0
3D	11.0	11.7	3.7	2.5	1.6	30.5	3I	1.5	4.6	13.6	36.0	6.5	62.2
4D	7.0	6.8	3.1	2.1	1.5	20.5	4I	1.4	3.5	7.4	13.8	3.7	29.8
5D	4.3	4.2	2.4	1.9	1.2	14.0	5I	1.3	2.7	4.3	6.8	2.3	17.4
6D	2.9	2.9	1.9	1.6	1.0	10.3	6I	1.1	2.0	2.9	4.1	1.6	11.7
2E	10.3	51.1	7.4	3.8	2.6	75.2	3J	1.2	2.9	8.4	36.6	5.4	54.5
3E	7.6	17.3	6.1	3.6	2.2	36.8	4J	1.1	2.4	5.6	14.1	3.6	26.8
4E	5.2	8.5	4.6	3.0	1.9	23.2	5J	1.0	2.0	3.6	6.9	2.3	15.8
5E	3.5	4.9	3.2	2.5	1.6	15.7	6J	0.8	1.6	2.5	4.1	1.6	10.6

Note: For left lateral field, columns IV and V are interchanged, but total doses remain the same.

TABLE II
ANTERIOR (BLADDER) PELVIC FIELD

Pelvic Position	Radium (10 mg.) Loading						Pelvic Position	Radium (10 mg.) Loading					
	I	II	III	IV	V	Total		I	II	III	IV	V	Total
3K	14.8	2.8	1.2	0.8	0.8	20.4	2P	5.6	54.5	16.7	5.0	5.0	86.8
4K	8.5	2.4	1.2	0.8	0.8	13.7	3P	5.0	17.3	10.6	4.1	4.1	41.1
5K	5.2	2.0	1.1	0.7	0.7	9.7	4P	4.0	8.5	6.3	3.1	3.1	25.0
6K	3.3	1.6	1.0	0.6	0.6	7.1	5P	3.1	4.9	4.0	2.2	2.2	16.4
3L	26.1	4.3	1.7	1.2	1.2	34.5	6P	2.3	3.1	2.7	1.7	1.7	11.5
4L	12.0	3.5	1.6	1.1	1.1	19.3	2Q	3.4	23.6	41.0	8.5	8.5	85.0
5L	6.0	2.7	1.4	1.0	1.0	12.1	3Q	3.2	12.0	16.2	6.4	6.4	44.2
6L	3.7	2.0	1.2	0.7	0.7	8.3	4Q	3.2	7.0	8.0	4.1	4.1	26.4
2M	84.9	9.8	2.4	1.5	1.5	100.1	5Q	2.3	4.2	4.7	2.8	2.8	16.8
3M	24.4	7.2	2.4	1.5	1.5	37.0	6Q	1.8	2.9	3.0	1.9	1.9	11.5
4M	11.2	5.1	2.2	1.3	1.3	21.1	2R	2.2	10.3	59.1	13.1	13.1	97.8
5M	5.9	3.5	1.8	1.1	1.1	13.4	3R	2.1	7.6	17.4	9.0	9.0	45.1
6M	3.6	2.4	1.5	1.0	1.0	9.5	4R	2.4	5.1	8.5	5.3	5.3	26.6
2N	25.4	22.2	4.0	2.1	2.1	55.8	5R	1.7	3.5	4.9	3.2	3.2	16.5
3N	14.6	11.7	3.8	2.0	2.0	34.1	6R	1.5	2.4	3.1	2.1	2.1	11.2
4N	8.5	6.8	3.1	1.7	1.7	21.8	3S	1.5	4.6	13.6	12.1	12.1	43.9
5N	5.1	4.2	2.4	1.4	1.4	14.5	4S	1.9	3.5	7.4	6.1	6.1	25.0
6N	3.3	2.9	1.9	1.2	1.2	10.5	5S	1.3	2.7	4.3	3.5	3.5	15.3
2O	10.7	51.8	7.6	3.1	3.1	76.3	6S	1.2	2.0	2.9	2.2	2.2	10.5
3O	8.7	17.1	6.3	2.8	2.8	37.7	3T	1.1	2.9	8.5	11.9	11.9	36.3
4O	6.0	8.5	4.6	2.2	2.2	23.5	4T	1.5	2.4	5.6	6.1	6.1	21.7
5O	4.1	4.9	3.2	1.8	1.8	15.8	5T	1.1	2.0	3.6	3.5	3.5	13.7
6O	2.8	3.1	2.3	1.4	1.4	11.0	6T	1.0	1.6	2.5	2.2	2.2	9.5

TABLE III
POSTERIOR (RECTAL) PELVIC FIELD

Pelvic Position	Radium (10 mg.) Loading						Pelvic Position	Radium (10 mg.) Loading					
	I	II	III	IV	V	Total		I	II	III	IV	V	Total
1K	34.9	2.1	0.8	0.6	0.6	39.0	6O	2.0	3.1	2.3	1.4	1.4	10.2
2K	19.3	2.8	1.0	0.8	0.8	24.7	2P	3.5	53.4	16.4	5.0	5.0	83.3
3K	10.2	2.8	1.1	0.8	0.8	15.7	3P	3.6	17.3	10.4	4.1	4.1	39.5
4K	5.9	2.4	1.2	0.8	0.8	11.1	4P	2.8	8.5	6.3	3.1	3.1	23.8
5K	3.7	2.0	1.1	0.7	0.7	8.2	5P	2.2	4.9	4.0	2.2	2.2	15.5
6K	2.5	1.6	1.0	0.6	0.6	6.3	6P	1.7	3.1	2.7	1.7	1.7	10.9
2L	35.0	4.8	1.4	1.2	1.2	43.6	2Q	1.9	23.6	41.0	8.5	8.5	83.5
3L	13.0	4.3	1.6	1.2	1.2	21.3	3Q	1.9	12.0	16.2	6.4	6.4	42.9
4L	6.8	3.5	1.5	1.1	1.1	14.0	4Q	1.9	7.0	8.0	4.1	4.1	25.1
5L	4.0	2.7	1.4	1.0	1.0	10.1	5Q	1.7	4.2	4.7	2.8	2.8	16.2
6L	2.7	2.0	1.2	0.7	0.7	7.3	6Q	1.4	2.9	3.0	1.9	1.9	11.1
2M	32.6	9.8	2.3	1.5	1.5	47.7	2R	1.3	10.3	58.9	13.1	13.1	96.7
3M	12.8	7.2	2.3	1.5	1.5	25.3	3R	1.3	7.6	17.5	9.0	9.0	44.4
4M	6.6	5.1	2.1	1.3	1.3	16.4	4R	1.3	5.1	8.5	5.3	5.3	25.5
5M	3.9	3.5	1.8	1.1	1.1	11.4	5R	1.2	3.5	4.9	3.2	3.2	16.0
6M	2.5	2.4	1.5	1.0	1.0	8.4	6R	1.1	2.4	3.1	2.1	2.1	10.8
2N	16.2	22.2	3.9	2.1	2.1	46.5	3S	1.0	4.6	13.6	12.1	12.1	43.4
3N	9.5	11.7	3.7	2.0	2.0	28.9	4S	1.0	3.5	7.4	6.1	6.1	24.1
4N	5.5	6.8	3.1	1.7	1.7	18.8	5S	1.0	2.7	4.3	3.5	3.5	15.0
5N	3.6	4.2	2.4	1.4	1.4	13.0	6S	0.8	2.0	2.9	2.2	2.2	10.1
6N	2.3	2.9	1.9	1.2	1.2	9.5	3T	0.6	2.9	8.4	11.9	11.9	35.7
2O	7.3	51.9	7.4	3.1	3.1	72.8	4T	0.6	2.4	5.6	6.1	6.1	20.8
3O	5.9	17.0	6.1	2.8	2.8	34.6	5T	0.7	2.0	3.6	3.5	3.5	13.3
4O	4.0	8.5	4.6	2.2	2.2	21.5	6T	0.6	1.6	2.5	2.2	2.2	9.1
5O	2.9	4.9	3.2	1.8	1.8	14.6							

standard type. On the evidence of calibration stability and repeatability of data, it is believed that the numerical values given are correct within approximately ± 3 per cent, or ± 0.1 r/hour, whichever is larger.

SUMMARY

Radiation dose distribution patterns around the familiar "double crossarm tandem" or "cross-tee" uterocervical radium applicator have been explored, using a commercially available type of ratemeter probe. Quantitative dose rate measurements, recorded at 1 cm. intervals in the lateral and anteroposterior planes, are presented graphically and also in tabular form. The use of such directly measured data, instead of multiple calculations from linear source tables, is expected to eliminate some

major errors caused by variable absorption in the metal structure of the applicator.

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NEW HYSTEROSTAT FOR RADIUM THERAPY IN ENDOMETRIAL CARCINOMA*

By G. F. GRANONE, M.D., and G. JULIANI, M.D.

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RECENT reports have again corroborated the usefulness of radiotherapy, either preoperatively or as the sole treatment, in carcinoma of the uterine body.^{1,3,4,12,23,27} Kottmeier¹⁹ records cure rates 14 per cent higher than those for surgery alone.

Heyman's packing method¹³⁻¹⁶ is now always considered the most suitable technique for intrauterine radium therapy. It is, nevertheless, felt that the new applicator or "hysterostat" here described may in certain cases be preferable to both the packing method and to other hysterostats.⁹ It is extremely simple to use and lends itself particularly well to accurate dosimetry.

The hysterostat is shown in Figure 1, *A* and *B*. Its diameter is equal to that of a No. 10 Hegar dilator and its weight is approximately 42 grams.

After dilating the cervix (with Hegar dilators up to No. 11) and, if necessary, performing diagnostic curettage, the hysterostat is introduced into the uterine cavity in the closed position (Fig. 2*A*). When the

fundus uteri is reached, the button tip is withdrawn by pulling out the rod handle at the lower end; the side arms are thus spread open so as to touch the internal wall of the uterus (Fig. 3*A*). The rod handle is then rotated to the left and pushed inwards. In this way the button tip is in the extended position, while the ferrule or "stop ring" remains at the base of the arms (Fig. 3*B*), keeping them firmly apart even during uterine contractions (Fig. 3, *B* and *C*). To remove the hysterostat, the rod handle is pulled outwards (so that the button tip is brought to rest on the ferrule), rotated back to the right and pushed forwards into the stem. The hysterostat is then withdrawn without difficulty.

In cases in which the uterine cavity is not symmetric, one of the arms of the hysterostat can be kept folded in the special lateral groove (Fig. 2, *B* and *C*). The technical details of the hysterostat have been given in a preliminary report.¹⁰ In Figure 4, *A* and *B*, the hysterostat is shown in use in a patient with endometrial carcinoma.

Two or three linear radium sources can

* From Istituto di Radiologia dell'Università di Torino, Italy (Direttore Professor E. Benassi).

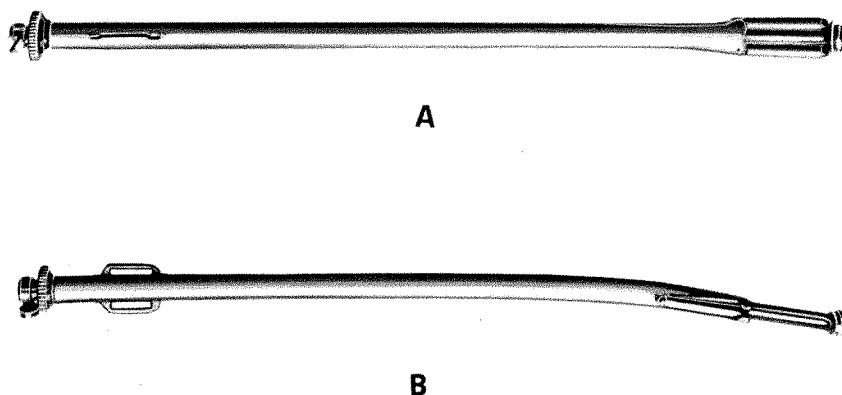


FIG. 1. (*A*) The hysterostat in the closed position seen from the front. (*B*) The hysterostat seen from the side with one arm folded along the side groove.

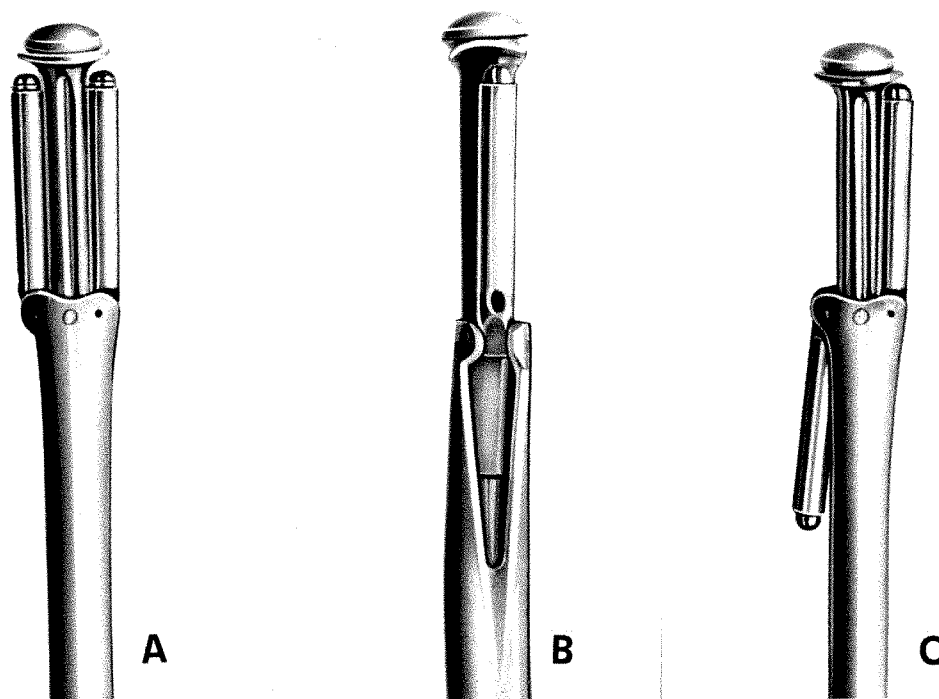


FIG. 2. Front view (A) and side view (B) of the hysteroscope in the closed position. Note the side groove in which one arm of the applicator can rest when not required. (C) Front view of the hysteroscope with one arm folded down.

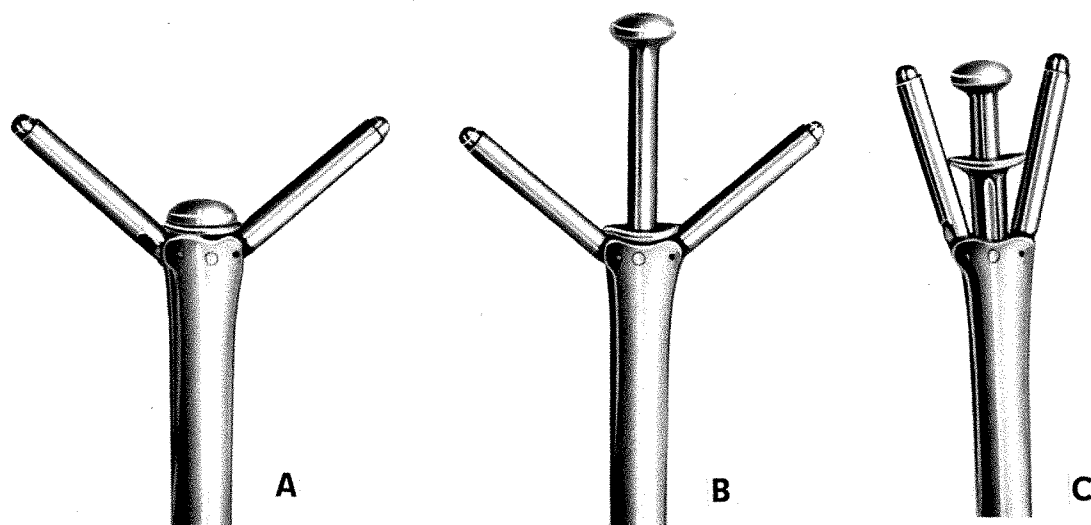


FIG. 3. (A) Front view of the hysteroscope with the arms spread apart and the button tip pulled down. (B) The button tip has been pushed forwards, leaving the metal ferrule between the arms and separating them firmly. (C) The hysteroscope with the arms spread apart in the intermediate position.

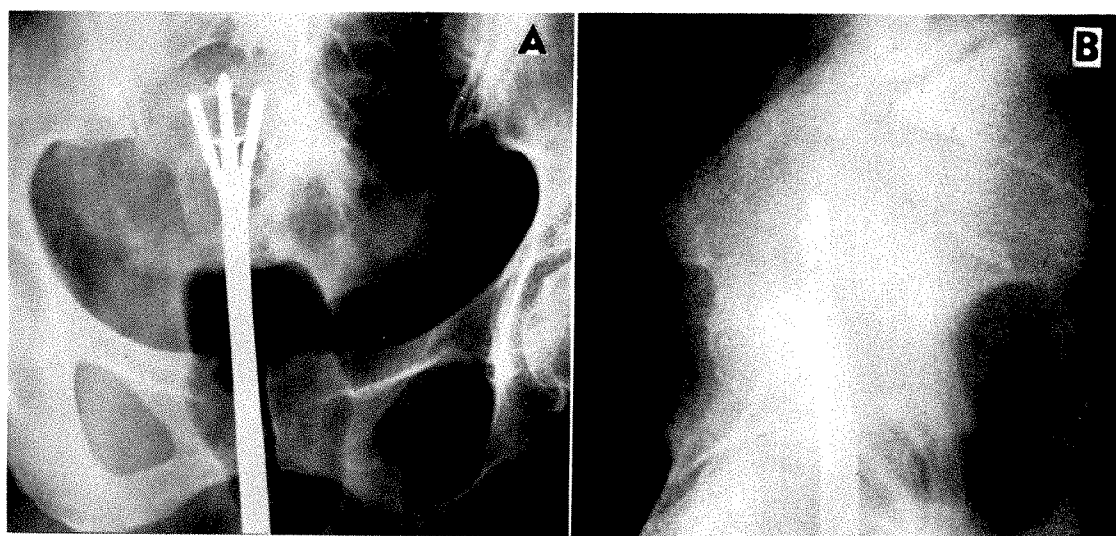


FIG. 4. The hysterostat in use in a patient with carcinoma of the uterine body; the arms are only slightly spread open. (A) Anteroposterior view; (B) lateral view.

be loaded in the central stem and two additional sources in the side arms. The authors prefer 20 mg. sources, each 22 mm. long, and filtration with 1 mm. of Pt.

Figure 5 is an isodose chart showing the dosage values found by using Greenfield and co-workers' tables.¹¹ With 20 mg. radium tubes and 1 mm. Pt filtration, the 100 per cent dose corresponds to 800 gamma r/hr.

Figure 6, A and B shows the experimental isodose charts obtained by direct measurement with a Siemens Gammameter and a plexiglass phantom. The dosimetry system employed was that used for a previous study, undertaken for a similar purpose and described in an earlier paper.¹⁷ The maximum measurable dose (that is, with the probe as close as possible to the hysterostat) is marked 100 and corresponds to 600 gamma r/hr. for 20 mg. tubes and 1 mm. Pt filtration.

In Figure 7, A, B and C autoradiographs which were obtained when 5 radium tubes were positioned in the hysterostat with the side arms spread open at right angles to each other are presented.

The findings obtained with the use of the three methods of dosimetry all point to the fact that the arrangement of radium sources

in the described applicator provides a uniform dose distribution, closely in keeping with the contours of a normal uterus. They also indicate that adequately high doses are delivered to the uterine angles and cervix,

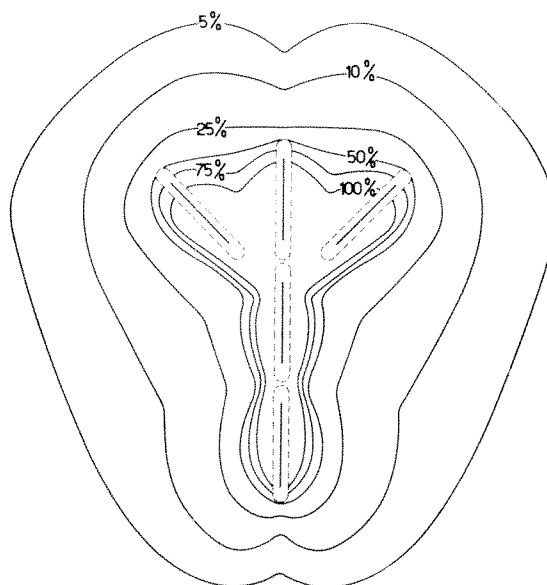


FIG. 5. Theoretic isodose curves constructed around 5 radium tubes containing equal loads and positioned as they would be in the hysterostat (in the open position). Dosage factors: 20 mg. tubes, 1 mm. Pt filtration: 100 per cent dose = 800 gamma r/hr.

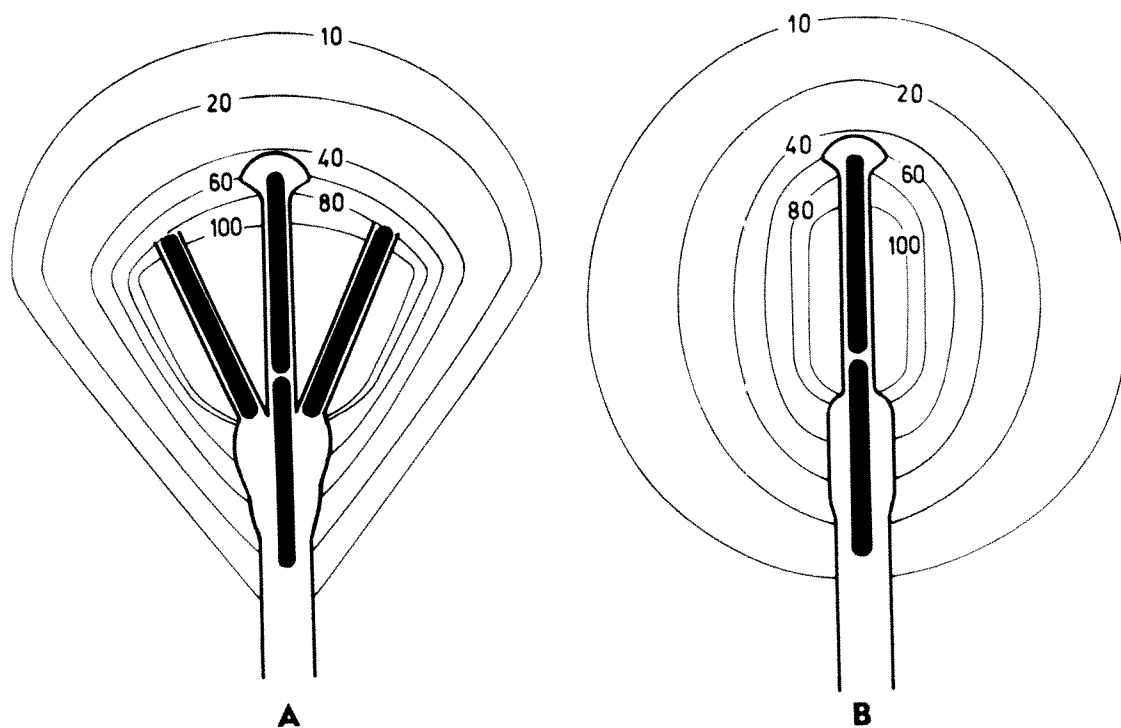


FIG. 6. (*A* and *B*) Experimental isodose curves measured with a Siemens Gammameter around the hystero-stat filled with 5 mg. tubes (100 = 150 gamma r/hr.).

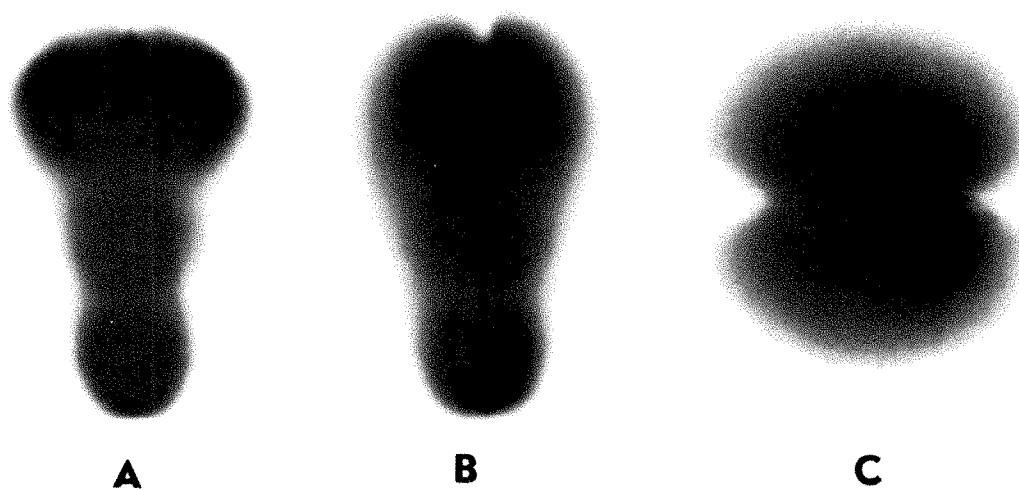


FIG. 7. Autoradiographs of five 5 mg. radium tubes placed as they would be in the hystero-stat with arms open at right angles to each other. (*A*) Frontal section; (*B*) sagittal section; (*C*) cross-section at the upper end of the three uppermost tubes.

the most common sites of neoplastic spread.

Absolute measurements suggest that with 20 mg. tubes in the hysterostat, effective treatment should take about 60 hours in all; the dosage schedule could, if necessary, provide for two 30 hour applications. With this schedule approximately 36,000 rads are delivered to the endometrium and approximately 7,000 rads to the outer surface of the uterus.

Direct bladder and rectal measurements showed negligible irradiation of these areas (3 and 2 per cent, or total doses of 1,000 and 650 rads, respectively).

SUMMARY AND CONCLUSIONS

1. The hysterostat described above consists of articulated parts operated mechanically.

2. It may be used in intrauterine radium therapy in cases of endometrial carcinoma in which the triangular shape of the uterine cavity is well preserved and also in asymmetric uterine cavities, when only one arm of the applicator is used.

3. Unlike the packing technique, the proposed method provides for the rapid insertion of the hysterostat. After dilatation of the cervix with a No. 11 Hegar dilator, the applicator is placed within the uterine cavity in a matter of seconds, with no risk to the operator and minimal trauma to the patient.

4. Isodose charting points to the therapeutic effectiveness of the source distribution provided by the applicator which ensures high doses to the uterine angles and cervix, the most common sites of neoplastic spread. Moreover, with the new applicator it is possible to achieve highly accurate and reliable clinical dosimetry.

5. Radiation to the bladder and rectum is negligible.

6. Effective anti-cancer treatment can be achieved in approximately 60 hours by using 20 mg. radium tubes.

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IONIZING RADIATION COLOR MEASUREMENTS OF THE HAP DOSIMETER*

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A SOLID chemical radiation detector containing a Halogenated compound, Azo dye and Paraffin matrix, HAP system, shows immediate color changes that are proportional to the amount of ionizing radiation absorbed by the in-phantom dosimeter. In two previous articles, in which certain characteristics and applications of this system were presented, radiation dose was estimated by gross visual inspection of changes in the yellow material itself or of changes as seen in photographs of the material.^{2,3} A third communication contained a preliminary report on quantitative methods for determining dose as a function of measured color.⁴ Lane, Johnson, and Bargoot¹ have described an ingenious technique in which they mapped isodose patterns around intracavitary radium sources by correlating HAP dosimeter color changes, as finally expressed on a photographic film, with thermoluminescent measurements, by lithium-fluoride dosimeters embedded in HAP material.

This paper presents direct quantitative relationships between the intensity of induced color and the amount of ionizing radiation. Color values represent measurements of reflected and transmitted light by photoelectric cell techniques. The effects of several physical factors upon sensitivity are discussed: dependence of a given dye to the wavelength of the measuring light, the role of filters, dosimeter thickness and light beam size. The extinction coefficient to light is calculated for dosimeters under analysis. Isodose patterns obtained by transmittance measurements of the HAP system are compared with standard depth-

dose tables and the accepted isodose curves for x-rays of the same quality.

MATERIALS AND EQUIPMENT

I. MATERIALS

Chloroform or bromoform dissolved in a paraffin base matrix were the primary components of the system. Three azo dyes served as indicators: p-dimethylaminoazobenzene, PDAB, $((CH_3)_2NC_6H_4N:NC_6H_5)$, 4-phenylazodiphenylamine, PADA, $(4-C_6H_5N:NC_6H_4NHC_6H_5)$ and p-phenylazoaniline, PPAA, $(NH_2C_6H_4N:NC_6H_5)$.

In the calculations of halogenated hydrocarbon molality, the matrix was considered to be the solvent. Thus, a one molal formula contained a mole of halogenated compound (e.g., 120 gm. chloroform) in a kilogram of paraffin based material. All agents were blended at 65 to 70° C. and the liquid mixtures were poured into molds to make translucent solid slabs or disks.

II. EQUIPMENT

A. For Transmittance Measurements. Figures 1 and 2 illustrate the apparatus used for transmittance measurements. A 2×4 cm. photoelectric cell of the self-generating barrier-layer variety* was placed in a circuit containing sensitivity controls for standardization in addition to a mirror-type galvanometer. To define the area of the dosimeter to be analyzed, the photoelectric cell was enclosed in a black metal container with a variable aperture and colored filters, which served as the search unit.

* Model 610, Photovolt Corporation, New York, N. Y.

* Presented at the Sixty-third Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 2-5, 1962.

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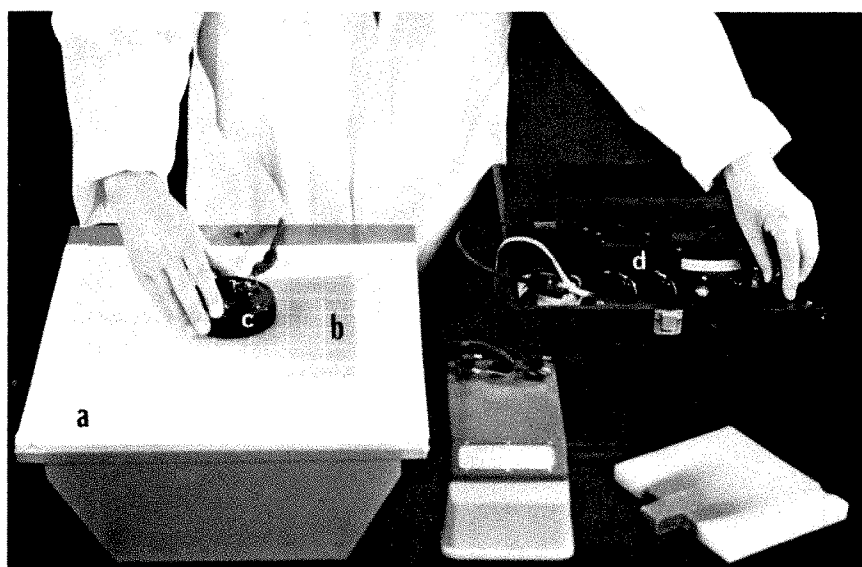


FIG. 1. Photograph of light transmittance measuring equipment: (a) light source, (b) dosimeter slab, (c) photoelectric search unit, and (d) sensitivity and calibration controls. The galvanometer is in the mid lower foreground.

The galvanometer scale was 85 mm. long with 100 divisions and the instrument showed a linear response to the amount of light from divisions 5 through 90. Fluorescent lamps operating at 118 volts A.C. through a voltage regulator were used to provide a light source of constant intensity. This source was fitted with variable size openings and colored filters to control the light incident upon and through the dosimeter.

Isodose patterns were measured on slabs of dosimeter by a phototube having spec-

tral intensity responses similar to those of the human eye. This search unit was equipped with a preamplifier which gave the system a sensitivity 100 times greater than the barrier-layer arrangement.

B. For Reflectance Measurements. A more complex probing head was needed for these studies (Fig. 3). The search unit had to contain its own light source as well as the pick-up or measuring barrier-layer photoelectric cell. The light source was a small incandescent lamp supplied with 6 volts A.C. from a constant voltage transformer.

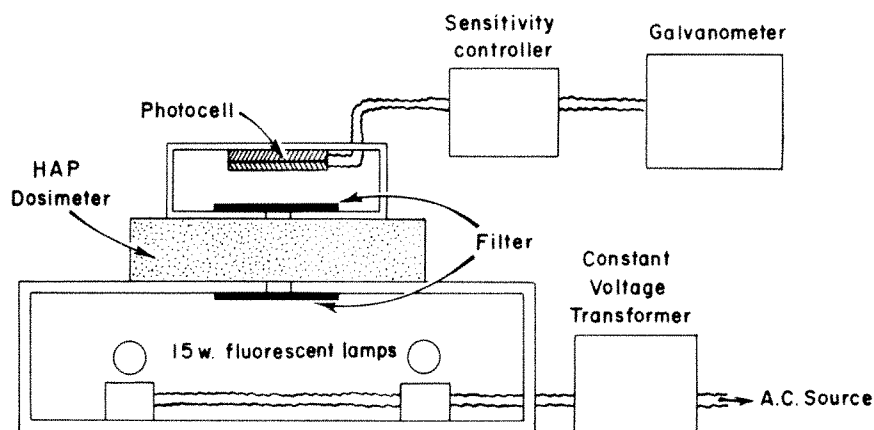


FIG. 2 Schematic diagram of instruments and material shown in Figure 1.

A second barrier-layer photoelectric cell served as a compensating device. Various colored filters and a white enamel calibrated standard were employed.

C. Radiation Sources. A resonant transformer x-ray machine was used at 280 kvp. to deliver radiation with a half value layer of 1.5 mm. Cu. Gamma radiation of greater penetration was obtained from a 1,500 curie cobalt 60 teletherapy unit. Except for the larger isodose-pattern slabs which were exposed through 4×6 cm. fields at target-to-surface distances of 50 cm., all HAP dosimeter disks were irradiated in 8×8 cm. fields at a source-to-surface distance of 70 cm. The output of each of these sources was checked with a Victoreen r-meter calibrated by the National Bureau of Standards.

METHODS AND RESULTS

I. REFLECTANCE TECHNIQUE

The galvanometer was standardized by a white enamel plaque having a reflectance of 73 per cent for green light and 74 per cent

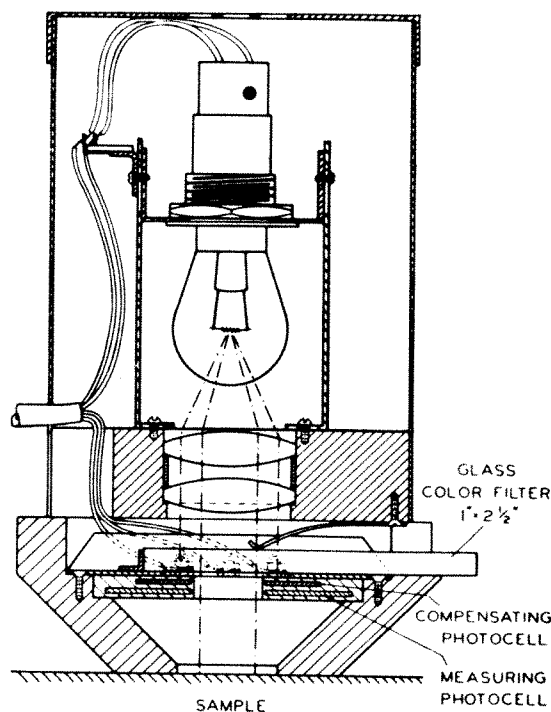


FIG. 3. Cross-sectional view of probing head for reflectance measurements.

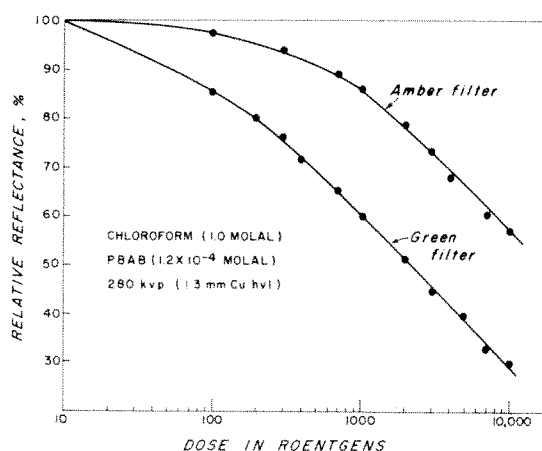


FIG. 4. Relative reflectance-exposure dose relationships for two types of filters. The 20 mm. thick dosimeter had p-dimethylaminoazobenzene as the dye.

for amber light. A search unit containing the coaxial-shaped photo-voltaic cells was placed directly on the surface of the dosimeter, which rested on black paper to prevent light backscatter from the table. The ratio of meter reading after irradiation to the meter reading before irradiation was defined as the relative reflectance. With azo dyes relative reflectance was reduced as the dose increased.

A green filter was found to yield greater sensitivity than an amber filter, as shown by the data of Figure 4.

As might be expected a comparison of techniques using reflected light with methods using transmitted light shows a lower sensitivity for the reflectance method, probably because less of the dosimeter is subjected to measurement. Minor surface imperfections also distort the color patterns resulting in a curvilinear response at low doses, whereas with medium and high doses the response is linear.

II. TRANSMITTANCE TECHNIQUE

The area of the dosimeter to be measured was placed over the hole in the mask covering the light source. The sensitivity of the method could be varied and the effect of dosimeter thickness compensated by means of the sensitivity controls on the meter, the aperture sizes and the kind of filters used

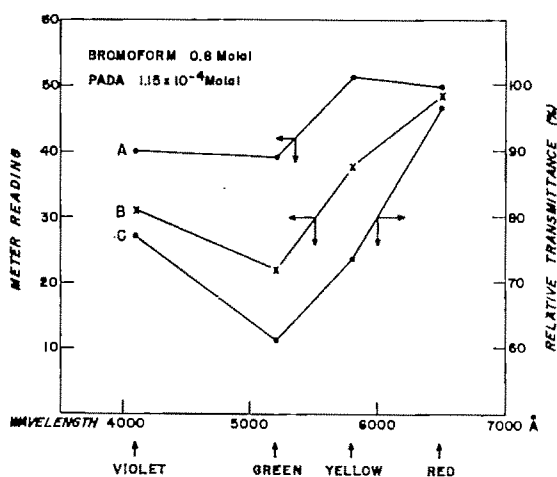


FIG. 5. Transmitted light intensity as a function of wavelength. A represents an unirradiated disk of dosimeter; B represents a disk having received 300 r; C gives the relative transmittance for the x-irradiated dosimeter. All disks were 5 mm. thick. The azo dye was 4-phenylazodiphenylamine.

over search unit and light source. Most measurements have been expressed as relative transmittance which is defined as follows:

% relative transmittance

$$= \frac{\text{meter reading after irradiation}}{\text{meter reading before irradiation}} \times 100.$$

A. Spectral Dependence. Transmitted light intensity was measured as a function of wavelength. Spectral dependence for the 4-phenylazodiphenylamine-bromoform system is shown in Figure 5 with similar responses found for p-dimethylaminoazobenzene and p-phenylazoaniline. These studies indicated that the greatest absorption of light or the biggest differential between the nonirradiated and irradiated disk measurements occurred in the green portion of the spectrum.

B. Filter Combinations. The effect of different filter combinations correlated well with the spectral responses as seen in Figure 6, which shows that green-green combinations allow the best sensitivity. However, even though the sensitivity was increased by green filters in both places, in some instances the p-dimethylaminoazobenzene

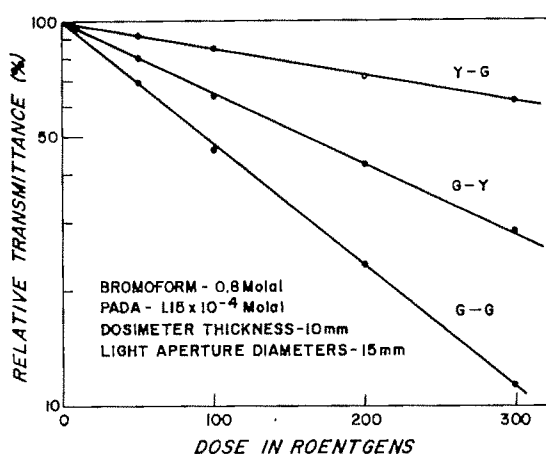


FIG. 6. Effect of filters on sensitivity expressed as log relative transmittance in relation to radiation dose for bromoform with 4-phenylazodiphenylamine. Y means yellow and G means green with the first letter indicating the kind of filter at the light source and the second letter the filter in front of the photocell.

response was nonlinear. It was made linear with a green filter at the light source and a yellow filter in front of the photoelectric cell. From the graphs in Figure 7, it is clear that the green-green combination gives a concave shape to the log R.T. vs. dose

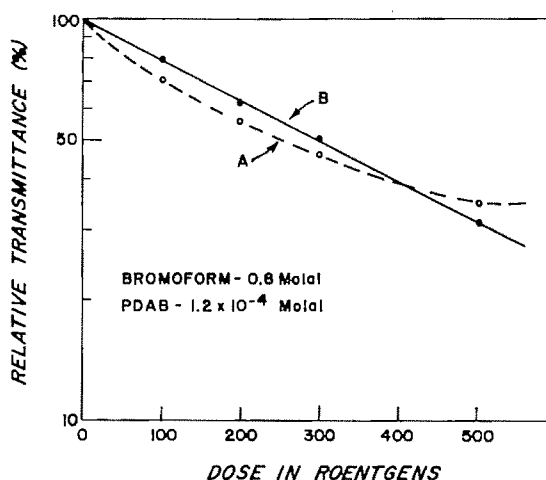


FIG. 7. Filter color-linearity relationship of bromoform with p-dimethylaminoazobenzene. The curves show log relative transmittance as a function of exposure dose for a 10 mm. thick dosimeter. A represents green-green and B green-yellow.

curve. Since linearity of the curve was desirable for practical reasons, various sets of filters were tried until the right ones were found. The graphs also show that at higher radiation doses the filter combinations responsible for linearity can turn out to be the most sensitive.

C. Light Beam Size. The dimensions of the light beam influence the sensitivity of the HAP dosimeter. Within the limits of this experiment the smallest apertures gave the highest dosimeter sensitivities (Fig. 8). Sizes smaller in diameter than 15 mm. were not explored because the photoelectric cell arrangement did not have the necessary response to the low photon intensities associated with the narrower light beams.

D. Dosimeter Thickness. It was logical to assume a greater sensitivity with an increase in dosimeter thickness, and this indeed was found to be the case (Fig. 9). Chloroform and bromoform dosimeters of 5, 10 and 15 mm. thickness were exposed to 280 kvp. x-rays (1.5 mm. Cu half value layer) and gamma rays from a cobalt 60 teletherapy unit. The results showed that in order to obtain a specific relative transmittance (e.g., 50 per cent) the 5 mm. dosimeter needed twice the dose required for the 10 mm. disk and three times the expo-

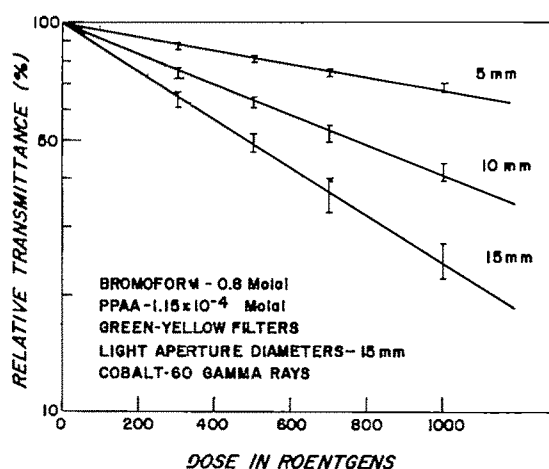


FIG. 9. Effect of dosimeter thickness on sensitivity log relative transmittance as a function of cobalt 60 exposure dose in roentgens for a bromoform formulation with p-phenylazoaniline. Graph shows the standard deviation for three separately prepared series of disks.

sure in roentgens used for the 15 mm. thick dosimeter. These findings were true for the same HAP composition and the same type and quality of radiation.

The relationships described above could be expressed with the following formula:

$$T = k(t \times D)$$

where T is the relative transmittance in per cent, k is a constant value due to dosimeter composition, radiation quality and instrument settings, t is thickness in millimeters and D is the radiation exposure in roentgens. These relationships held at chloroform molalities from 0.5 to 2.0 and bromoform molalities from 0.4 to 1.6 for all three azo dyes. Figure 10 shows the effect of doubling the halogenated hydrocarbon or dye concentration on sensitivity in relation to dosimeter thickness. It is important to realize that it had been shown previously that an increase in halogenated hydrocarbon concentration increases the degree of color change for a given radiation dose within rather definite limits.⁴ Further and more extensive studies on this most interesting phenomenon will be presented in a subsequent paper.

E. Light Extinction Coefficient. Attenua-

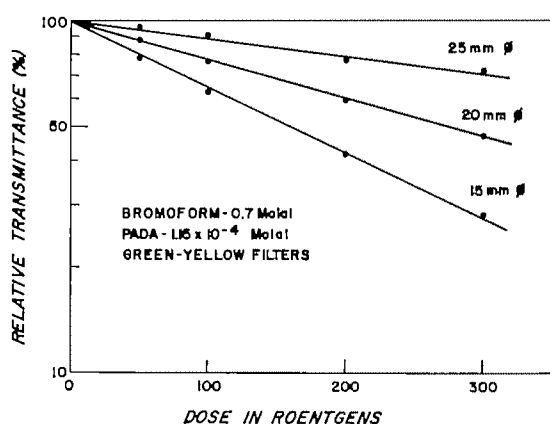


FIG. 8. Effect of light beam size on sensitivity expressed as log relative transmittance as a function of exposure dose in roentgens. In each case the diameter of the window at the light source and the search unit were the same for the measurements on 10 mm. thick disks.

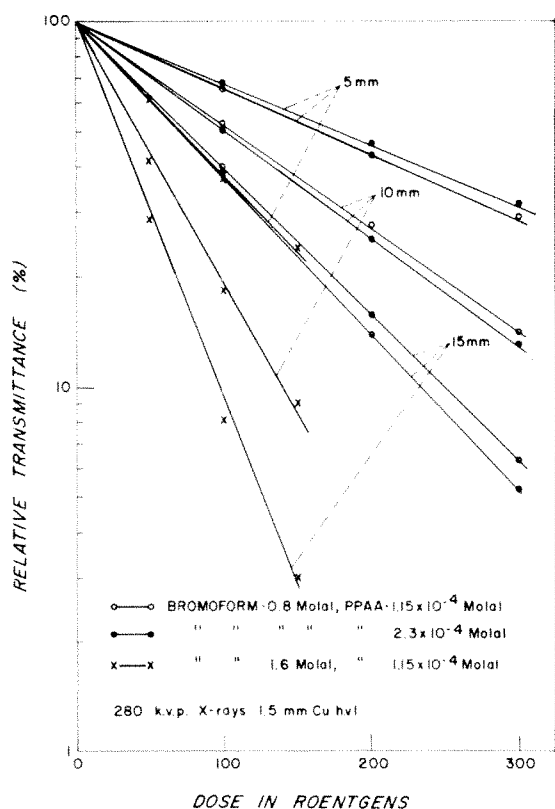


FIG. 10. Effect of dosimeter thickness and chemical concentrations on sensitivity of bromoform-PPAA formulations.

tion rate of the visible light as it was absorbed and scattered by the dosimeter being analyzed was measured and expressed as the extinction coefficient. In addition to x- and gamma-ray quality and dose on the extinction coefficient, the effects of chloroform, bromoform and azo dye concentrations were studied before and after irradiation.

Light extinction coefficient curves for the chloroform systems were linear when expressed as a function of increased exposure dose of x- or gamma-rays (Fig. 11 and 12). As a rule, the bromoform systems behaved similarly (Fig. 13 and 14); however, Figure 15 illustrates that the x- and gamma-ray responses of bromoform-azo dye systems of the same molality may not be linear in all instances. P-phenylazoaniline and 4-phenylazodiphenylamine showed straight-line responses, while p-dimethylaminoazobenzene

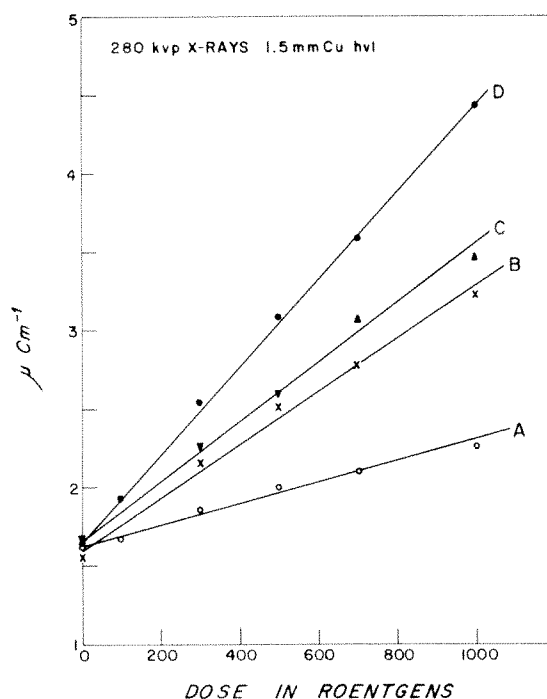


FIG. 11. Extinction coefficients as a function of dose (280 kvp. x-rays, 1.5 mm. Cu half value layer). A: Chloroform 1.0 molal, PDAB 1.15×10^{-4} molal. B: Chloroform 1.0 molal, PADA 1.15×10^{-4} molal. C: Chloroform 1.0 molal, PADA 2.3×10^{-4} molal. D: Chloroform 2.0 molal, PADA 1.15×10^{-4} molal.

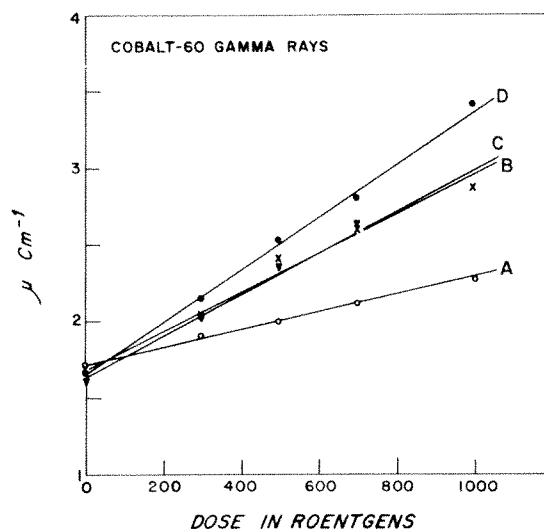


FIG. 12. Extinction coefficient as a function of dose (cobalt 60 gamma-rays). A: Chloroform 1.0 molal, PDAB 1.15×10^{-4} molal. B: Chloroform 1.0 molal, PADA 1.15×10^{-4} molal. C: Chloroform 1.0 molal, PADA 2.3×10^{-4} molal. D: Chloroform 2.0 molal, PADA 1.15×10^{-4} molal.

was curvilinear for 280 kvp. x-rays. This bromoform p-dimethylaminoazobenzene behavior to x-rays was repeated several times and analyzed with different filters but always with the same result. The reason for this deviation is not known.

It is evident that dye concentrations affect the slope of the extinction coefficients very little, whereas different concentrations of the halogenated compound have a much larger effect.

The results indicate that the light extinction coefficient increases on the basis of the following formula:

$$\mu = \mu_0 + \alpha D$$

where μ_0 is the initial extinction coefficient before irradiation in cm^{-1} , α is the increment of light extinction coefficient per

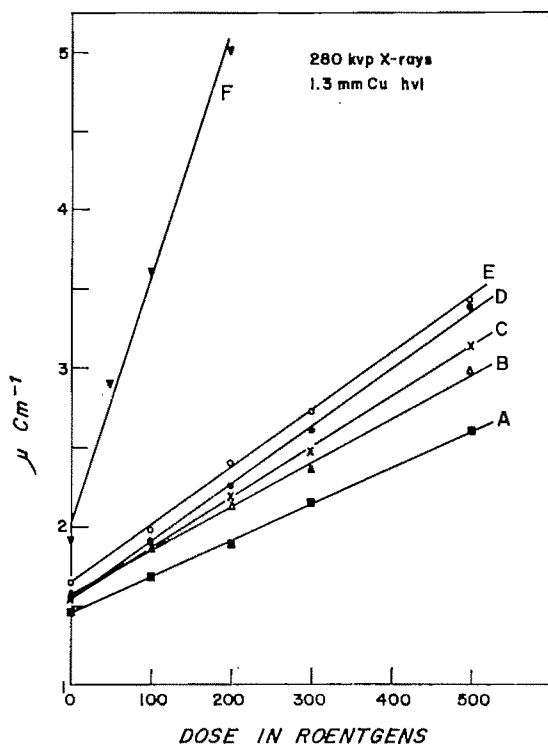


FIG. 13. Extinction coefficient as a function of dose (280 kvp. x-rays 1.3 mm. Cu half value layer). Bromoform molal concentrations: A=0.4; B, C, D, and E=0.8; F=1.6. PPAA (1×10^{-4}) molal concentrations: A, C, and F=1.15; B=0.58; D=2.3; E=4.6.

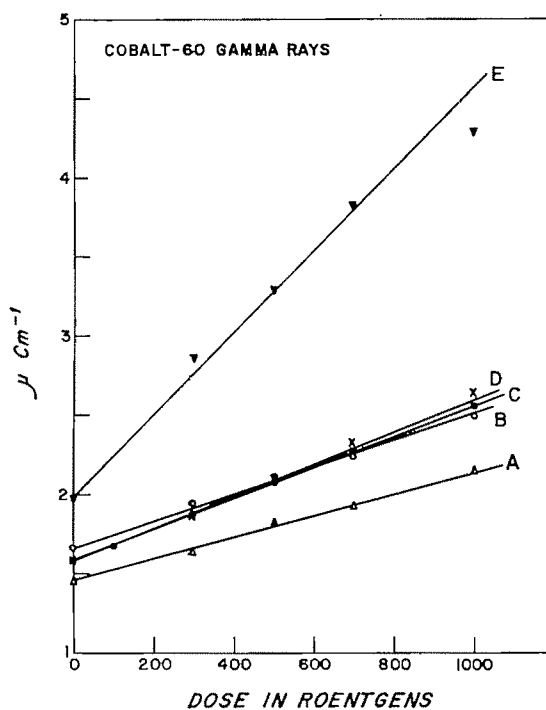


FIG. 14. Extinction coefficient as a function of dose (cobalt 60 gamma-rays). Bromoform molal concentrations: A=0.4; B, C, and D=0.8; E=1.6. PPAA (1×10^{-4}) molal concentrations: A=1.15; B=4.6; C=2.3; D=4.6; E=1.15.

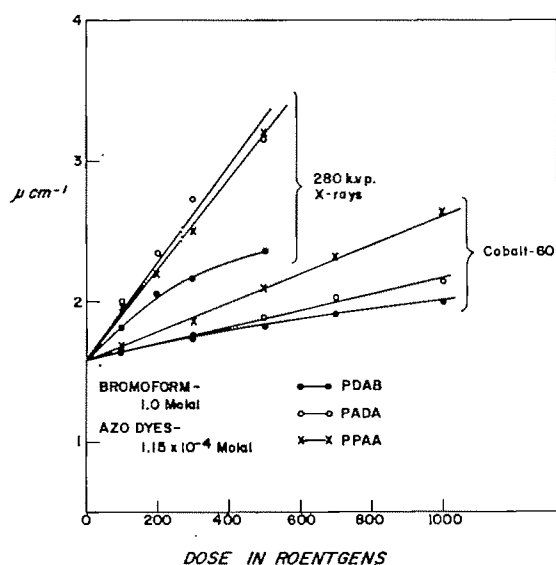


FIG. 15. Comparison of extinction coefficients of azo dyes (280 kvp. x-rays 1.3 mm. Cu half value layer and cobalt 60 gamma-rays).

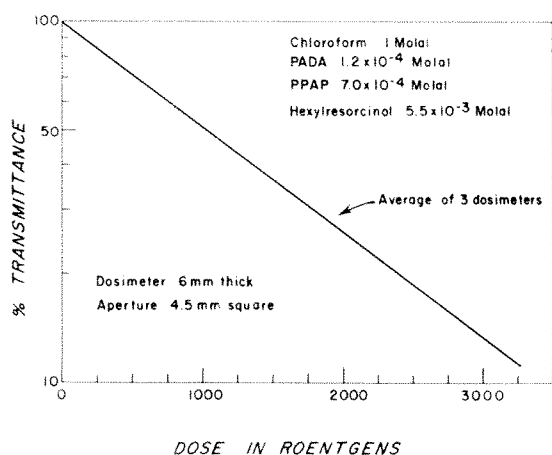


FIG. 16. Standard reference curve which was used for isodose plotting. Three series of identically prepared dosimeter disks were exposed to different amounts of radiation and the color change measured as log per cent transmittance or log relative transmittance.

roentgen in cm^{-1} , and D is the exposure dose in roentgens.

Consequently, it is proper to assume that the relative transmittance decreased according to this formula:

$$R.T. (\%) = 100 \times e^{-(\mu_0 + \alpha D)t}$$

where t is the thickness of the dosimeter in centimeters. Therefore, the transmittance can be corrected for variations in thickness for systems of identical composition and the dose calculated for a given dosimeter thickness.

III. ISODOSE CURVES

To compare the isodose patterns as determined from measurements of the HAP dosimeter with the generally accepted isodose curves, a one molal slab of a chloroform dosimeter was prepared using 4-phenylazodiphenylamine as the dye in a concentration of 1.15×10^{-4} molal. Hexylresorcinol in 5.6×10^{-3} molal concentration and p-phenylazophenol in a 5.75×10^{-4} molal concentration were added for reasons of stability.

A large block made up of several dosimeter slabs was irradiated with a surface dose of 1,500 r of 280 kvp. x-rays through a

4×6 cm. portal at a target-to-surface distance of 50 cm. From the central part of this phantom, a 6 mm. thick slab was removed and the color changes were analyzed. Figure 16 shows measurements obtained for three sets of dosimeters that were exposed to known quantities of the same x-rays. This graph served as a reference standard for the dose calculations in the slab having the dose distribution pattern. The actual isodose curves are presented in Figure 17, which shows findings through the long axis of the 4×6 cm. field.

DISCUSSION

It is clear from these studies that the right type of photoelectric cell is essential if practical measurements of color change in the HAP dosimeter are to be obtained. The spectral response and the sensitivity must fall within specific limits, even though

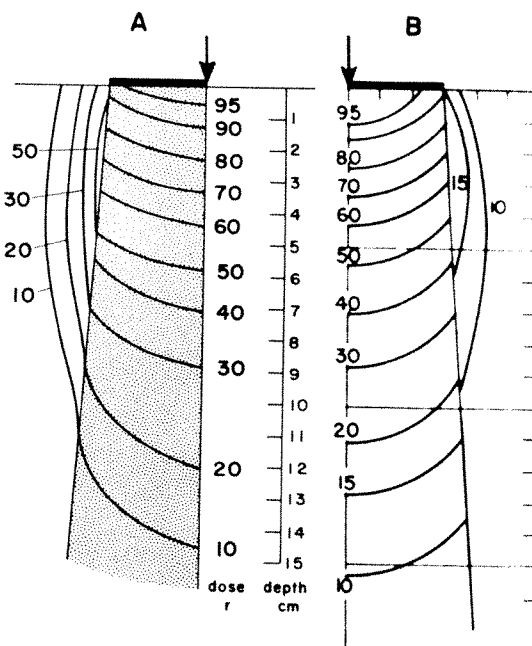


FIG. 17. Comparison of isodose curves obtained with the HAP dosimeter (A) with a generally accepted set of isodose curves (B) for x-rays having a half value layer of 1.3 mm. copper. The HAP dosimeter was 6 mm. thick and contained the following molal concentrations: Chloroform 1.0; 4-phenylazodiphenylamine 1.15×10^{-4} ; p-phenylazophenol 5.75×10^{-4} ; and hexylresorcinol 5.6×10^{-3} .

analysis of the dosimeter can be enhanced with the proper filters.

Light beam size influenced the sensitivity of the HAP dosimeter. Plans are underway to use a highly sensitive photomultiplier search unit in probing the effects of very small diameter light beams. With some dyes the smaller beams seemed to give a more linear response. This apparent difference in sensitivity and linearity with change in light beam diameter may reflect a difference in the ratio of the light absorbed and the light scattered by the translucent dosimeter as seen by a particular photoelectric cell.

In many discussions concerning electromagnetic radiation attenuation in its passage through particular materials, the rate of decrease in the intensity of a beam of photons is usually referred to as the absorption coefficient. The term is often used erroneously for there has been a failure to recognize more than one cause for the decrease in the light intensity. In general, there are two principal types of attenuation that light, x-rays and gamma-rays experience upon entering a body of matter. A larger or smaller part of the radiation will be subjected to scattering, being reflected in all directions, while the remainder is absorbed by being converted into other forms of energy. In many instances the scattered radiation may still be effective in the same ways as the original; however, the absorbed portion ceases to exist as electromagnetic radiation. In the case of HAP dosimeter measurements, it is important to distinguish between the true absorption coefficient and the scattering coefficient, so for practical purposes the two are added together as the total attenuation or the extinction coefficient.

From precise measurements of radiation which has passed through various thicknesses of a substance, it has been determined that an infinitely thin layer of the medium perpendicular to the direction of the electromagnetic wave propagation reduces the radiation flux density by a fraction of its value proportional to the thick-

ness of the layer, and by integration the flux density can be calculated for a given penetration of the material according to the following formula:

$$I = I_0 e^{-\alpha x}$$

where x is the distance traversed in the medium, and I_0 is the flux density immediately after entrance into the medium ($x=0$). The constant, α , can be either the absorption coefficient, the scattering coefficient or represent the total attenuation as the extinction coefficient.

The extinction coefficient may be determined for the total radiation which enters the attenuating medium or it may be calculated for certain wavelengths as a spectral extinction coefficient. Through the use of filters, the extinction coefficient is applied to a narrower band of wavelengths, thereby enhancing the contrast or widening the difference between unirradiated and irradiated dosimeters.

A careful study of the isodose patterns in Figure 17 reveals a close similarity between the HAP dosimeter and a standard reference set of curves. However, there are differences that have appeared each time the experiment has been conducted. The midline or central axis doses are in fairly good agreement but the slope of the isodose curves is different. Also, scatter outside of the direct beam is much more pronounced in the HAP dosimeter. The reasons for these discrepancies of dose distribution between the two methods is not known, but some speculations can be made.

One possibility is that there is nonuniformity in the dosimeter composition. Another possible answer is that because of the chlorine or bromine we are seeing a Z effect. An explanation that must also be included is based on the kind of radiation that affects the HAP dosimeter as compared to what affects an ionization chamber. The HAP system will see and measure photons with energies capable of producing ionization down to photons in the ultraviolet and even in the visible light range. Thus the HAP dosimeter sees the original

radiation plus much of the "degradation" radiation. An ionization chamber will measure only the photons of higher energy or those capable of passing through the wall of the chamber.

If the latter explanation has any validity, then the effect should be greater at lower x- and gamma-ray energies. The impression is that this may be the case. It would also seem that the value of these formulations as accurate dosimeters for biologic systems might be open to question. However, after careful consideration there is reason to believe that the HAP dosimeter may even give a truer index of radiation effects in living tissue. We know that ultraviolet light can profoundly affect living cells and lately more reports are appearing about the damaging properties to certain cells of photons in the visible light range. Perhaps, a significant part of radiobiologic phenomena is the result of ultraviolet and visible light photons that are attenuation products of the original ionizing radiation. Living cells deep in tissues may possibly be sensitive to these less energetic photons that are not usually measured. More studies are underway in an attempt to clarify some of the questions that have arisen.

CONCLUSIONS

1. The solid in-phantom HAP dosimeter (Halogenated compound-Azo dye-Paraffin base) can be quantitatively analyzed for color changes as a function of radiation

dose using photoelectric cell techniques.

2. Reflectance and transmittance measurements of light intensity can be used. The relative transmittance technique is more sensitive and more practical.

3. Log relative transmittance and extinction coefficients (sum of absorption and scatter coefficients) as a function of ionizing radiation dose, in general, display a graphic linearity.

4. Isodose patterns obtained by measuring colors in irradiated HAP systems have compared favorably with the standard curves for the same radiation quality. The central axis doses were in reasonably good agreement, but away from the midline there was a difference in the shape of the isodose contours for the two methods.

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THE EFFECTS OF CHEMICAL CONCENTRATIONS AND CHEMICAL MODIFIERS ON THE HAP DOSIMETER*

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HALOGENATED compounds and indicators in a high molecular weight organic matrix have been found to fill many criteria of a practical in-phantom dosimeter.^{2,3,4,5} Particularly useful have been HAP dosimeters consisting of Halogenated hydrocarbons and Azo dyes in Paraffin. Gamma-rays, x-rays, electrons and protons have caused the portions of the phantom exposed to ionizing radiation to undergo immediate color changes which have been proportional to absorbed dose. It has been shown previously that the colors of the dosimeter, before and after irradiation may be quantified and accurately correlated with radiation dose.⁶

One of the advantages of the HAP system is the ease with which electron density and \bar{Z} values can be changed and made closely equivalent to soft tissue. Fortunately, varying the composition in such a way that it approximates animal or human soft tissue affects the sensitivity favorably in that, low halogenated hydrocarbon concentration systems and consequently more desirable solid formulations exhibit the greatest change in radiation-induced color. Since it has been established that, in this kind of system, the halogenated hydrocarbon is probably the agent undergoing radiolysis, these findings appear to deviate from Beer's law. For example, 2 dosimeters having chloroform in the same matrix with the same dye should absorb the same amount of measuring light after the same amount of ionizing radiation if one has twice the mole concentration of chloroform but is one-half the thickness of the other. With the HAP system this does not occur.

This deviation from Beer's law is striking, as has been previously shown and reported.^{5,6} Quantitative experimental data on these observations, the effects of dye concentrations and studies concerned with chemical agents modifying the behavior of the HAP dosimeter will be presented in this paper.

MATERIALS AND EQUIPMENT

Chloroform and bromoform were the halogen compounds mixed in a paraffin matrix. The three dyes, 4-phenylazodiphenylamine (PADA), p-dimethylaminoazobenzene (PDAB), and p-phenylazoaniline (PPAA), were used as indicators. One azo dye, p-phenylazophenol was employed as a sensitivity-modifying chemical. The main groups of modifying agents were alcohols and phenols. Several alcohols were studied and these were: ethyl, benzyl, heptyl, methoxybutanol, phenylbutanol, hexanediol, ethylnonanol, dimethylcyclohexanol, and dihydroxymethylbutane. The phenols were as follows: phenol, resorcinol, hexylresorcinol and pyrogallol.

The photoelectronic measuring instruments were those described in the preceding article. Dosimeter formulations were exposed to x-ray (280 kvp., 1.5 mm. Cu half value layer) and gamma-ray (cobalt 60) sources.

RESULTS

A. Effects of Halogenated Hydrocarbon Concentrations on Sensitivity. Several molal concentrations of chloroform and bromoform were examined for radiation-induced color intensity using each of the three azo

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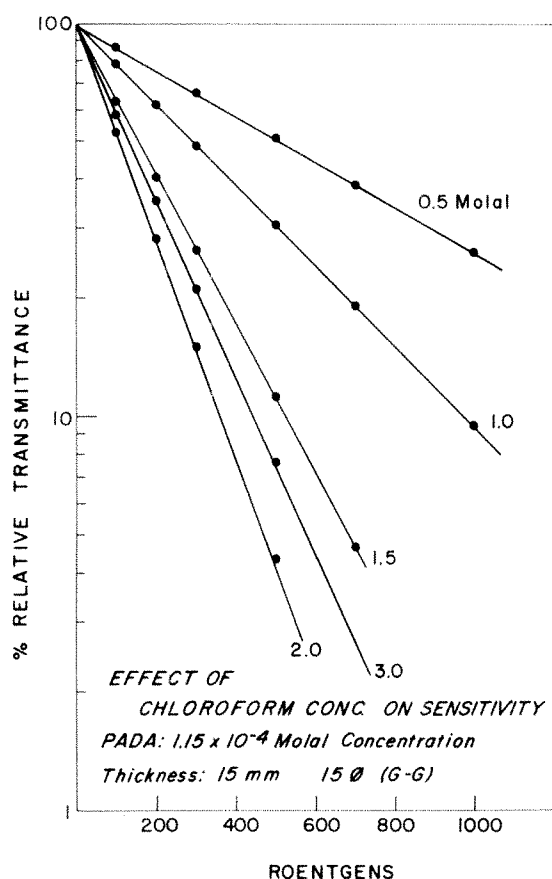


FIG. 1. Effect of chloroform concentration on sensitivity. The steeper the curve, the greater the sensitivity.

dyes in the same 1.15×10^{-4} molal concentration. Figures 1 and 2 show the data obtained with 4-phenylazodiphenylamine. The graphs shown in Figures 3 and 4 were obtained by determining the dose of x-rays necessary to reduce the relative transmittance to 37 per cent.

These studies indicated that 1.5 to 2.0 molal concentrations of chloroform and 4.0 to 6.0 molal concentrations of bromoform resulted in the greatest measurable change in color. With chloroform, 4-phenylazodiphenylamine was most sensitive in all ranges of halogenated hydrocarbon concentrations, but, with bromoform in concentrations lower than 3.0 molal, p-phenylazobenzene was best and, at concentrations above 3.0 molal, 4-phenylazodiphenylamine gave the greatest sensitivity. Of the three

dyes p-dimethylaminoazobenzene held intermediate or less sensitive positions in most instances.

B. Effects of Dye Concentration on Sensitivity. All three azo dyes were tested for sensitivity in concentrations ranging from 0.6 to 2.4×10^{-4} molal in systems containing 1.0 and 1.5 molal concentrations of chloroform, and were examined also in the same way as for the studies on halogenated hydrocarbon concentration effects. The relative transmittance was measured as a function of exposure dose in roentgens in 15 mm. thick dosimeters. The sensitivity of each dye concentration was likewise compared by determining the dose required to reduce the relative transmittance to 37 per cent.

The findings showed that dye concentra-

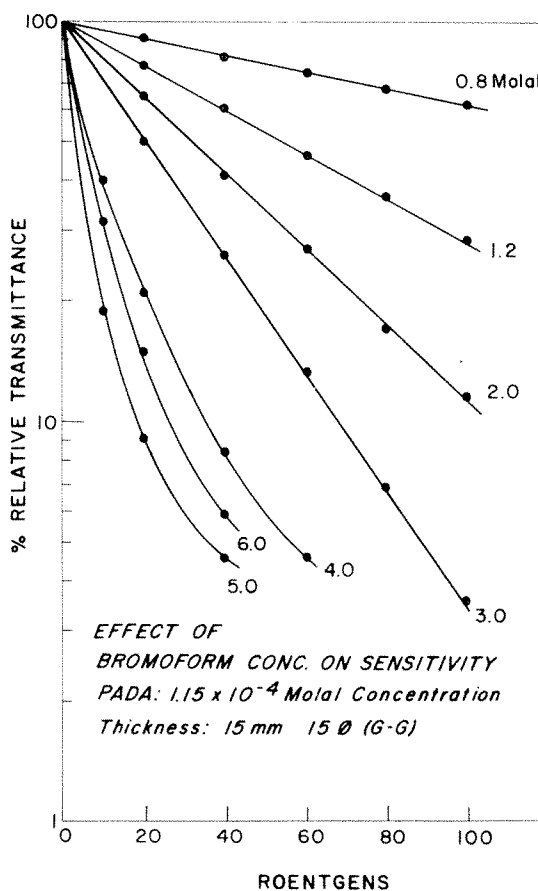


FIG. 2. Effect of bromoform concentration on sensitivity.

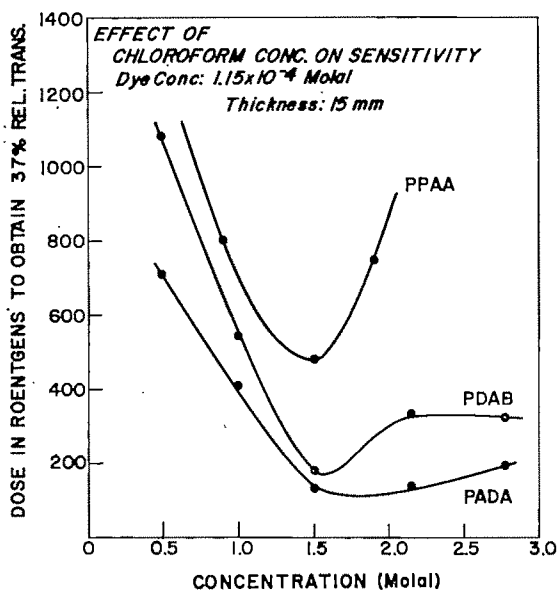


FIG. 3. Effect of chloroform concentration on sensitivity expressed as x-ray dose required to reduce the transmission of measuring light from 100 to 37 per cent.

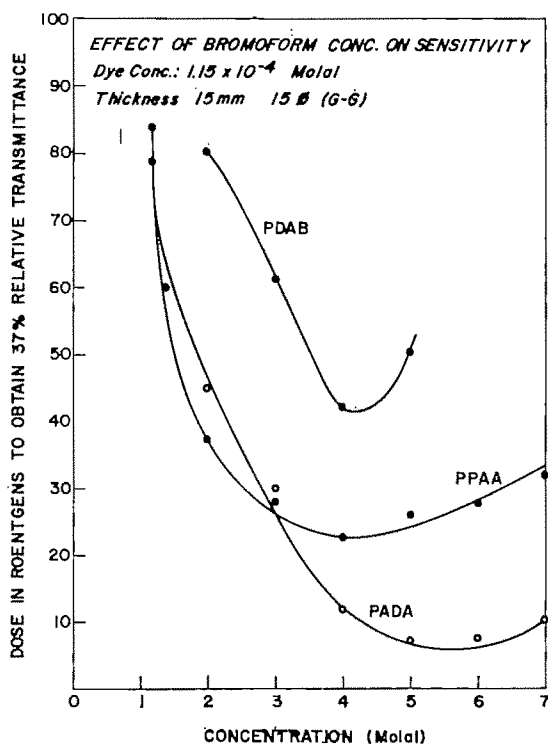


FIG. 4. Effect of bromoform concentration on sensitivity expressed as x-ray dose required to reduce the transmission of measuring light from 100 to 37 per cent.

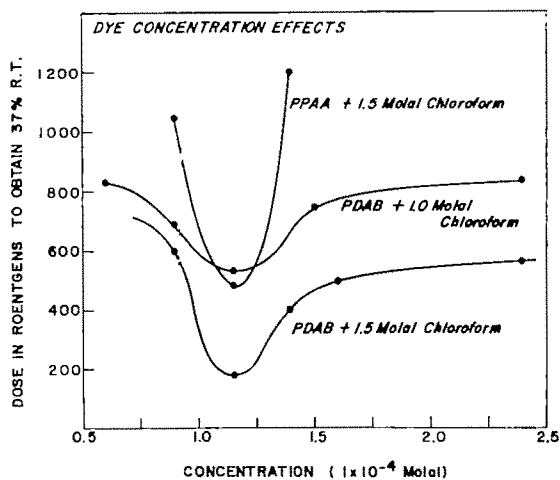


FIG. 5. Effect of dye concentration on sensitivity expressed as x-ray dose required to reduce measuring light transmission from 100 to 37 per cent in chloroform. A comparison of the 1.0 molal formulation with the 1.5 molal dosimeter indicates the pronounced effect of halogenated hydrocarbon concentration.

tions generally had less of an effect on sensitivity than chloroform and bromoform concentrations. As shown in Figures 5 and 6, two dyes, p-dimethylaminoazobenzene and p-phenylazoaniline, had peak responses

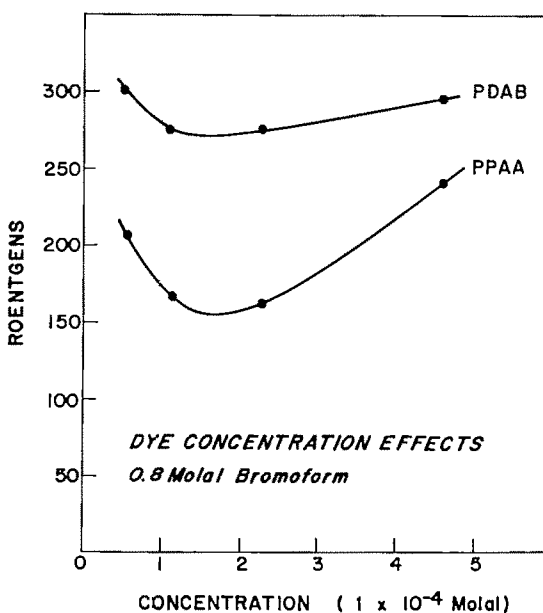


FIG. 6. Effect of dye concentration on bromoform formulation.

at about 1.15×10^{-4} molal concentration for both concentrations of chloroform, and peak responses between 1.5 and 1.8×10^{-4} molal concentrations for the bromoform system. The dye, 4-phenylazodiphenylamine, was most striking in its response as it gave a rather flat and linear curve for the concentrations studied and affected sensitivity the least.

C. Effects of Alcohols. The following alcohols were added in various amounts to systems containing chloroform or bromoform and one of the three azo dyes: dimethylcyclohexanol, ethylnonanol, heptyl alcohol, butanediol, hexanediol, methylbutanol, phenylbutanol, dihydroxymethylbutane, benzyl alcohol and ethyl alcohol. Methyl alcohol could not be tested because of its low boiling point. Relative transmittance measurements of color intensity were made as described above.

With the exception of benzyl alcohol, these agents did not affect the sensitivity significantly when used up to concentrations of about 1 to 2 molal. Higher concentrations decreased the sensitivity of the dosimeter. All alcohols increased color-holding, that is, they protected the dosimeter against color fading with time. Benzyl alcohol was the only one of this group of agents that increased the sensitivity of the HAP system. A 1 molal chloroform system with 4-phenylazodiphenylamine containing 0.1 molal benzyl alcohol required approximately 15 per cent less x-ray exposure to produce the same intensity of color change in the dosimeter. Dihydroxymethylbutane and benzyl alcohol exhibited the best color-holding properties of the alcohols examined.

D. Effects of Phenolic Compounds. Phenol, resorcinol, hexylresorcinol and pyrogallol in various concentrations were tried in bromoform systems of 0.2 and 0.8 molal and chloroform systems of 1.0 and 2.0 molal. Two azo dyes, p-dimethylaminoazobenzene and 4-phenylazodiphenylamine, in 1.15×10^{-4} molal concentrations were the indicators.

All the phenolic compounds listed above

enhanced radiation-induced color changes. As little as 1×10^{-3} molal of resorcinol caused the sensitivity of the chloroform system to rise approximately 50 per cent, whereas it took about 5×10^{-3} molal of hexylresorcinol to accomplish a similar effect. Increasing the concentration of phenols much beyond the levels mentioned for the resorcinols raised the levels of sensitivity and absolute gain relatively little. These agents also showed good color-holding properties though they also increased the sensitivity of the dosimeter to sunlight. Of this group of phenols, hexylresorcinol was the easiest to dissolve in the dosimeter and was the best as a protector against color fading after irradiation.

Hexylresorcinol had another valuable and interesting property of protecting the different formulations against the deleterious effects of small concentrations of pure water on radiation-induced colors. It takes only 0.001 per cent of water by weight in a HAP formulation without a protecting and stabilizing agent to eliminate all or nearly all of the radiation-produced color. Even with less than 0.001 per cent water, the color would fade in a matter of minutes. Water has been one of the strongest chemical modifiers of the HAP system and had been responsible for many confusing inconsistencies that were originally observed. A 5×10^{-3} molal concentration of hexylresorcinol has protected the dosimeter against 0.5 per cent water by weight as shown in Figures 7 and 8. All water-contaminated dosimeters that were studied had their sensitivity, stability, and reproducibility restored by hexylresorcinol.

E. Effects of Phenolic Azo Dye. Another fascinating chemical modifier was p-phenylazophenol, both an azo dye and a phenol, which was found to reduce the sensitivity of the dosimeter to sunlight and still permitted the system to retain, and in higher concentrations even increase slightly, the sensitivity to ionizing radiation. As an indicator by itself, it was not useful but in combinations with other azo dyes it improved certain characteristics of the HAP

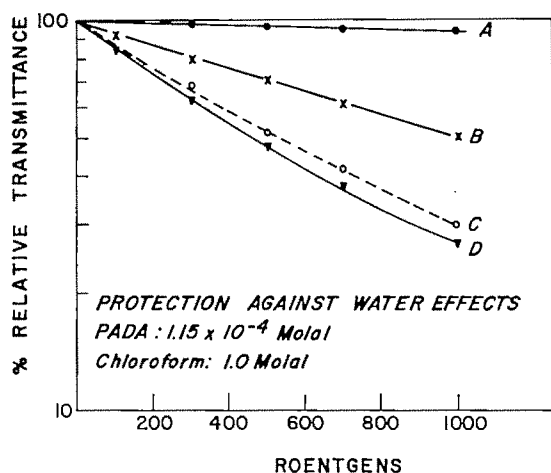


FIG. 7. Protection against water effects. A had 0.1 per cent water added; B had no additions; C had 0.1 per cent water and contained 5×10^{-3} molal concentration of hexylresorcinol; and D contained 5×10^{-3} molal hexylresorcinol without the addition of water.

system. This protection to photons in the ultraviolet range, but not to more energetic radiation (Fig. 9 and 10), was more pronounced with chloroform than with bromoform and was not significantly affected by doubling the concentration of chloroform. The effects of 0 to 12.0×10^{-4} molal concen-

trations of p-phenylazophenol (PPAP) were examined in formulations containing 1.2×10^{-4} molal of p-dimethylaminoazobenzene (PDAB) and 4-phenylazodiphenylamine (PADA) as indicators. The concentrations of chloroform were 1.0 and 2.0 molal and when bromoform was the halogenated hydrocarbon it was in a 0.2 molal concentration.

A ratio was used to express the length of sunlight-exposure time needed to change the color of the dosimeter so the transmission of measuring light through it was reduced 10 per cent. The exposure ratio was obtained by taking the time required to reduce relative transmittance from 100 to 90 per cent with p-phenylazophenol and dividing that by the time required to obtain the same value in a dosimeter without PPAP (time for conc. x/time for conc. o). One set of findings is presented in Table 1. It was also found that concentrations of p-phenylazophenol over 6.0×10^{-4} molal gave the unirradiated dosimeter an initial color that was a deeper yellow than desired and this resulted in dose distribution patterns of lower contrast.

In the next set of experiments, 5.0 and

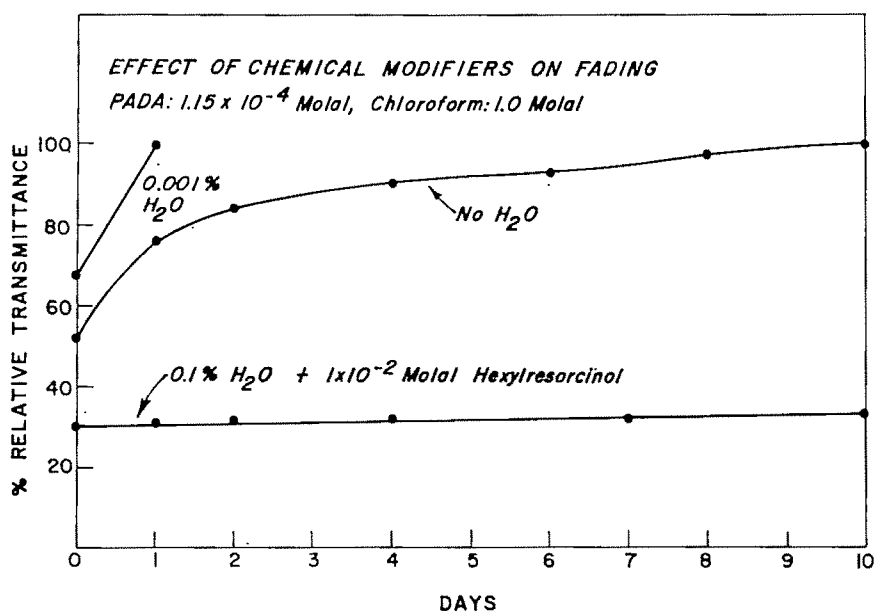


FIG. 8. Effect of chemical modifiers on fading. Note the fine stability of the hexylresorcinol system.

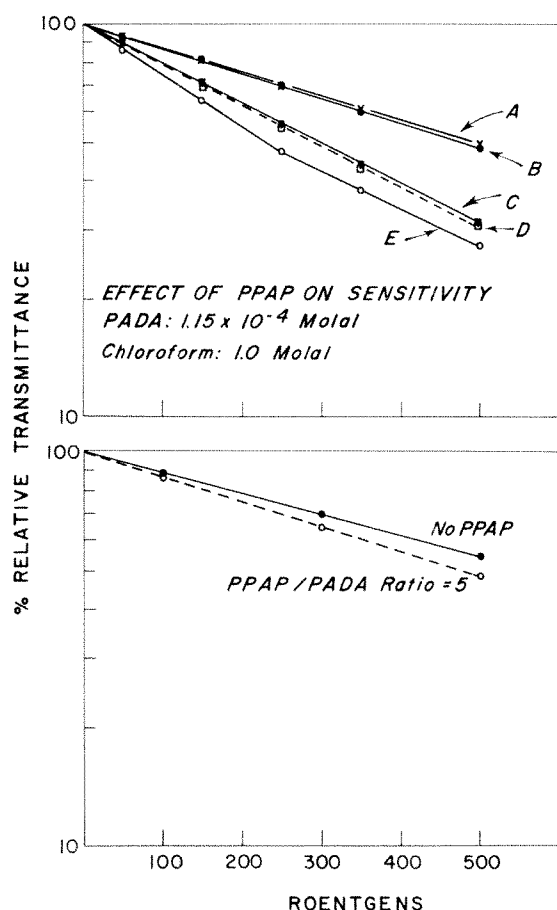


FIG. 9. Effect of p-phenylazophenol and hexylresorcinol on sensitivity to x-rays. A has a molal concentration of PPAP that is three times that of PADA; B is a formulation without PPAP or hexylresorcinol; C contains five times as much PPAP as PADA with the addition of 5×10^{-3} molal hexylresorcinol; D contains three times as much PPAP as PADA and a 5×10^{-3} molal concentration of hexylresorcinol; and E has 5×10^{-3} molal hexylresorcinol but no PPAP.

10.0×10^{-3} molal concentrations of hexylresorcinol were added to the same chloroform and bromoform dosimeters containing p-phenylazophenol. Hexylresorcinol continued to exert its radiation sensitivity-enhancing properties while it retained its color-holding characteristics without eliminating the protective effect of PPAP. These findings are shown in Tables II and III, and Figures 9 and 10.

DISCUSSION

Low concentrations of halogenated hydrocarbon in the HAP system have consistently produced more color change from a given radiation dose than high concentrations. This is an unexpected finding because it has been long established that the radiolysis of chloroform will result in acid production,¹ and, the higher the concentration of halogenated hydrocarbon subjected to the same amount of radiation in dosimeters, the more acid there should be and the more color change there should be in the indicator. The observed phenomena might appear to deviate from Beer's law in terms of the relationship of amount of halogenated hydrocarbon breakdown due to radiation, and the degree or amount of color

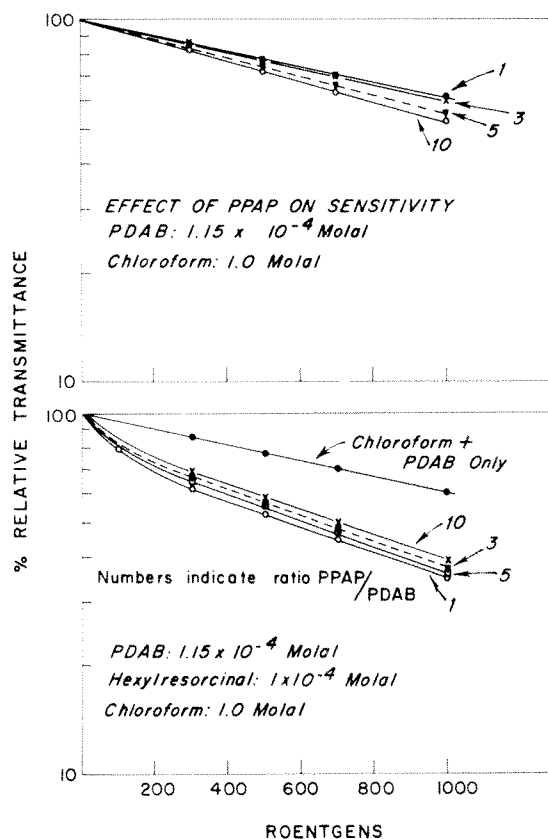


FIG. 10. Effect of p-phenylazophenol with and without hexylresorcinol on sensitivity of the HAP system to x rays.

PPAP PROTECTION OF HAP DOSIMETER
TO SUNLIGHT(10 mm. thick dosimeters containing 1.0
molal chloroform)TABLE I
(1.2×10^{-4} molal PDAB)

PPAP (1×10^{-4} molal)	0	1.2	3.6	6.0
Exposure Ratio	1	4.0	15.0	30.0

TABLE II
(1.2×10^{-4} molal PDAB and 5.0×10^{-3}
molal hexylresorcinol)

PPAP (1×10^{-4} molal)	0	3.6	6.0	12.0
Exposure Ratio	1	15.0	25.0	100.0

TABLE III
(1.2×10^{-4} molal PADA and 5.0×10^{-3}
molal hexylresorcinol)

PPAP (1×10^{-4} molal)	0	3.6	6.0
Exposure Ratio	1	13.0	24.0

change recorded. This may be considered a deviation if it is accepted that Beer's law can be applied to such solid chemical systems.

Preliminary experiments have been conducted to determine the amount of acid produced with various concentrations of halogenated hydrocarbon by a given dose of x-irradiation. Solid HAP systems with paraffin as the matrix and liquid systems with heavy mineral oil, instead of paraffin as the base, were treated with distilled water to extract acids that were formed. Titration and pH measurements indicated strongly that acid production was directly proportional, or nearly so, to the concentrations of chloroform and bromoform. This has meant that the acid is formed but is not manifesting itself proportionately as a color change in the indicator dye.

The degree of color change may simply be a matter of variations in the physical state of the solid dosimeter as brought

about by the different concentrations of the halogenated hydrocarbon with a resultant change in the color centers, perhaps in much the same way as a highly chromatic crystal can be powdered to lose color and become almost white. Another possibility is that, at certain concentrations of halogenated hydrocarbon, dye and matrix, an optimum physical situation exists to create a complex that permits the best formation of color centers. There are reasons to suspect the latter in that the amount of color with low halogenated hydrocarbon concentrations is often so pronounced.

As part of other pilot studies, hydrochloric acid gas was dissolved in alcohol and identical amounts of this mixture were placed in HAP formulations containing different amounts of chloroform. Under these conditions the peak color change was again seen in the 1 and 2 or low molal concentrations as shown in Figure 1. Perhaps, also in further support of the idea suggesting formation of a better color complex, may be the fact that dye concentrations also exhibited a small but definite peak response even in optimal concentrations of chloroform and bromoform.

Methane and its halogenated derivatives have an unusual ability to attract water and form hydrate microcrystals. Chloroform and bromoform possess these properties. The profound effects of small quantities of water in the HAP system may be explained on the basis of a disruption of delicate spatial relationships of the components by hydration or an attempt at hydration of the halogenated hydrocarbon. Hexylresorcinol, by blocking the profound effect of water in eliminating radiation-induced colors, may be preventing the hydration of chloroform and bromoform. Without a protective agent such as a phenol, the radiation-formed acid may have more affinity for the water than the dye.

In a sense, alcohols and phenols reinforce the color complex or color center. These same compounds have been used as stabilizers in aqueous chloroform chemical radia-

tion dosimeters, but, when they are used in those systems, the sensitivity or radiation-induced color is less. In the paraffin base formulations, the phenols, especially, increase the sensitivity and the color yield. The effects of these agents are completely opposite in aqueous systems as compared to the non-aqueous HAP dosimeters.

The protective effect of p-phenylazo-phenol against photons in the ultraviolet range but not against more energetic x-ray photons is somewhat baffling. Just how that compound might have something to do with a color center complex or just how it might dissipate or absorb the energy of ultraviolet photons without a color change is difficult to picture. More investigation is needed on this most fascinating phenomenon.

CONCLUSION

In the solid matrix HAP chemical dosimeter:

1. The concentration of halogenated hydrocarbon shows a peak response to radiation that permits a favorable sensitivity in formulations approaching soft-tissue equivalence.
2. The dye concentration influences the radiation-induced color change but in a manner that is less significant.
3. Alcohols stabilize the dosimeter color

and in a few instances increase the dosimeter response to radiation.

4. Phenols not only increase dosimeter sensitivity and prevent color fading but can eliminate the deleterious effects of trace amounts of water.

5. At least one phenolic azo dye seems to have the most unusual property of influencing the HAP system differently for ionizing and non-ionizing electromagnetic radiation.

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BASIC CONCEPTS AND DESIGN OF A TOTAL INFORMATION STORAGE AND DATA EXTRACTION SYSTEM FOR RADIOISOTOPE SCANNING*

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MANY devices and techniques have been both proposed and used to date for the visualization of the distribution of radioisotopes in internal body organs. Unfortunately, no adequate criteria of operational performance have been established and the judgment of a particular system has been almost entirely subjective. It is the purpose here to describe a philosophy of approach, a working system that we feel performs in a manner superior to most systems available today, and, finally, the clinical results illustrating the principles involved.

Stated succinctly, our objective has been to design a system by which all information received by the detector with little or no distortion can be stored permanently and conveniently, and which later allows the rapid extraction of the original data with ancillary devices to enhance the visual detection of the size and shape of any abnormalities. It is not to be implied that we have an optimum system since the problem is very complex and not all facets have yet been specified or analyzed—particularly those relating the detector response to the true organ distribution.

BASIC CONSIDERATIONS

Generally, one is not only concerned with the distribution of radioisotopes in the volume of the organ but also with the detection of abnormalities in such a distribution. While this implies a thorough study of normals, it also demands an understanding of the problems inherent in detecting small differences. Since the original signal is ran-

dom in time, the problem reduces to a consideration of the statistics of detecting a randomly varying signal in a randomly varying background. This is not quite the same as is usually considered in communication theory where random "noise" disguises an absolute "signal." In general, the statistical variations in the signal itself must always be considered and the addition of noise (collimator leakage, scatter, tube noise, etc.) appears as more signal of the same character.

Any system containing the above limitations due to statistics must necessarily involve judgment on the part of the observer as to the significance of any particular observation. While clinical considerations may give special weight and impact to any observation, such should enter in only after statistical significance has been established.

Many systems have been designed to present the data for ready analysis. The simplest is the use of "profiles" which are graphs of count-rate versus position for a large number of "slices" through the organ. While these profiles represent all the available data, the process of reconstructing the distribution in the original organ is laborious and time consuming. If one does compound such profiles,⁴ one obtains a "surface" whose undulations are a measure of the activity distributed in depth in the organ as detected by the collimator. This is still a two dimensional plot of the organ since the activity in depth may not bear any relation to the physical size of the organ in this dimension. Collimator characteristics are of extreme importance when at-

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tempting to assess this third dimension. Under any circumstance, this method of presenting a surface uses the eye as a simple auto-correlation device to establish that a given change in one profile is significant since other nearby profiles had an equivalent change that indicated a geometric abnormality of a given size. It is important to keep in mind, however, that scanning the same area with a larger collimator that produces one profile would establish the presence of an abnormality with equal significance. Multiple scans with a smaller collimator reduce the statistical accuracy of each profile but the resultant profile surface and an eye analysis produce about the same result with the added feature of determination of size of the abnormality. The clinician must decide on the compromise between detectability of deviation from normal and accurate outline, since increasing one diminishes the other for a given organ activity and scan time. Such a limitation arises because of the statistical nature of the signal combined with noise where increased resolution results in decreased counts with a corresponding increase in the statistical variations.

Photoscanning and "dot" or "dash" on paper are merely methods of presenting the above mentioned profile surface with variations in density or number of spots per unit area representing the signal in depth. Some investigators have resorted to color differences but the fact is that the dynamic range of the normal eye for color change is much smaller than that for intensity differences. The disadvantage of all these visual systems is that even though it is represented, the actual data in depth are generally lost and one has a more difficult task in assessing significance of any change. Visual aids such as contrast enhancement, background erase, etc., have been developed to assist the eye in detecting abnormalities in such presentations. It is to be emphasized that these never add any information and generally reduce it. While in certain cases this loss may not be important, it is irrevocable in most of the equipment today and re-

quires prejudgment on the part of the observer. A useful solution to this is total information storage prior to analysis. Such storage can be either short-time or long-time depending on the desires of the observer and his problems with records. Long-time total storage elements that may be attached to the patient's record are to be preferred.

STATISTICS, RESOLUTION AND DETECTABILITY

Recognizing the fact that a visual scan is simply another way of presenting a series of profile cuts, let us examine the statistics involved without reference to the capability of the collimator to define any particular abnormality. Consider a square collimator of effective side d and area d^2 projected on a plane containing radioactivity E counts per unit area per unit time over an area A . Also assume the total scan time to be T , with the scanning performed in lines a distance d apart. By definition the collimator "sees" a rate of α counts per minute, produces a total scan count of αT , and will present on any visual presentation a total count (or density equivalent thereto) of $\alpha T/A$, per unit area.

While the total information content involves d because of resolution, it is obvious that for a given d , the information content is proportional to ET . These parameters are generally fixed by clinical considerations. It is also obvious that for a given d , T , and E it theoretically makes no difference whether the adjacent line scans are just touching or a system of sub-integral overlaps is used. The only difference is the appearance (or apparent resolution) of the edge or a discontinuity in the direction of the line scan steps. The term "apparent" resolution is used since, for a point discontinuity, all that is reproduced are the characteristics of the collimator. The visual pattern has no resemblance to the actual discontinuity. Further, a discontinuity of length d will be reproduced as having a base $2d$ in length. To have the same apparent resolution vertically as one does horizon-

tally would require an infinite number of sub-integral overlaps. The visual record will reproduce the actual abnormality only when the abnormality is much larger (*i.e.*, a factor of 10 or more) than the projected size of the scanning aperture. Such an effect, however, can be of aid in assessing statistical significance since no recorded discontinuity can be smaller than the projected aperture.

If one plots a profile, the actual data are the detected count rate α modified by the time constant in the rate meter. Since scanning is really a motion of the viewing head, the resolution in the direction of scan may be represented by time, and the time required to move the head a distance d is obviously $T_s d^2/A_s$. If a rate meter with a time constant RC is subjected to a sudden change, a time

$$t_0 = RC[0.394 + (\frac{1}{2}) \ln 2\alpha RC]$$

is required for the output to come to an equilibrium differing from the new average value by less than one standard deviation.² Figure 1 is a graph of the relationship between t_0 and α for various RC . If one wishes to preserve the resolution of the collimator, then t_0 must be less than the time required

to scan d . How much less is a matter of judgment regarding resolution criteria and we shall assume a factor of 4. If the RC time is made longer, one gains in statistical accuracy at the expense of resolution. Loss in resolution will also affect the total information since numerically fewer large apparent defects can be presented in a given field. Another disadvantage that arises in visual presentation is that for large apparent defects, the eye is apparently more sensitive to sharp boundaries and edge gradients are naturally reduced by large time constants.

An interesting consequence of this time lag of count rate meters is that all scan lines should be traversed in the same direction since if they were traversed in alternate directions, alternate profiles would be displaced by $2t_0$ or a distance $d = 2t_0 A_s / T_s d$.

With the above limitation on time constant, it can be shown that the fractional standard deviation of the plotted output of the rate meter at any given time is F.S.D. $= (2\alpha RC)^{-1/2}$. Consideration of statistics tells us that 31.7 per cent of all observations will fall further than one standard deviation, 5 per cent further than two and 0.3 per cent further than three. If we assume that the shape of the apparent discontinuity will be an aid in identification (*i.e.*, minimizing spurious choices), we may propose that a new signal E' will be significantly different when it differs by more than 2 standard deviations from E . Thus the minimum observable fractional change is then $E - E' / E = 2(2\alpha RC)^{-1/2}$ where RC is determined by the condition $t_0 = T_s d^2 / 4A_s$. This is shown in Figure 2.

Some typical values for a liver scan with a single bore collimator are $\alpha \approx 40$ counts per second, $T_s \approx 2,400$ seconds, $A_s \approx 120$ square inches, and $d \approx 0.5$ inches. This leads to a $t_0 = 1.25$ seconds and $RC = 0.55$ seconds. From these, the minimum observable fractional change is 32 per cent. This is for the signal as seen by the detector. It is obvious that if the signal contains noise (background, leakage, scatter, etc.) a much larger change must occur in the isotope dis-

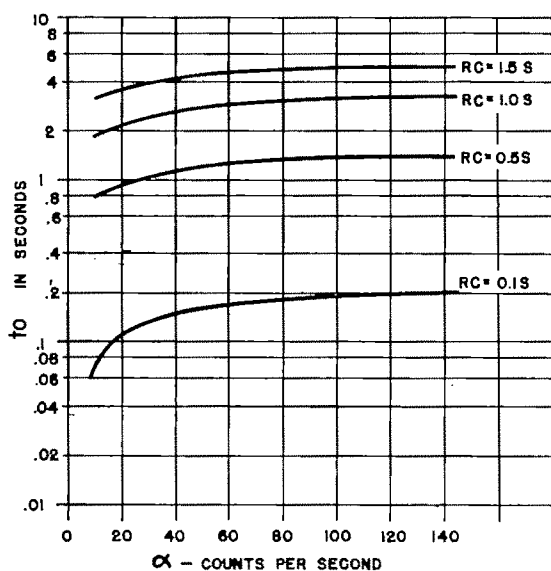


FIG. 1. Equilibrium time t_0 as a function of counting rate for various rate meter time constants.

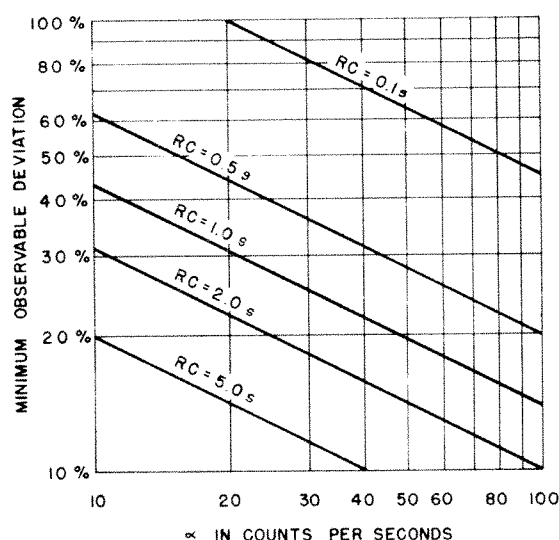


FIG. 2. Minimum observable deviation in a "profile" record as a function of counting rate for various rate meter time constants.

tribution before it can be observed on a profile. These limitations will be discussed in another paper.

In the above calculation, it is obvious that one is demanding a good resolution in the direction of the scan and a very poor one in the direction of the steps. Most investigators speed up the scan motion by a factor of 4 and use $d/4$ sub-integral steps. For the same RC time and total scan time, we see that the minimum observable fractional change for such a speed-up remains the same, but the vertical resolution is improved by a factor of 4 while the horizontal resolution is reduced by the same factor. This illustrates again the fact that for a given E and T_s , the total information remains constant and that all we do is change the manner of presentation.

If we now make a visual picture by recording all observed counts in their proper geometric areas of detection and if no time constants are involved, we have the problem of discerning an area equal to d^2 containing $\alpha'T_s d^2/A_s$ counts immersed in a uniform field of count density $\alpha'T_s d^2/A_s$ per d^2 area. Now data on the characteristics of the eye⁶ show that to be reasonably certain that a given observed area is not spurious,

the events in the observed area must differ by at least 4 standard deviations from the events in a similar area in the surrounds. For our case, this may be expressed as

$$\frac{E' - E}{E} \geq 4 \left[\frac{\alpha d^2 T_s}{A_s} \right]^{-1/2}$$

provided the picture is minified sufficiently that the eye integrates the counts over area d^2 . For the above data, this leads to a minimum observable fractional change of 27 per cent. Considering the assumptions involved, it is reasonable to conclude that both methods are equivalent and one can obtain the same information whether one compounds profiles or uses a total storage visual method.

One can show that the detected count rate of any cylinder (*i.e.*, straight bore collimator) is related to the effective collimator width d by the relation $\alpha = KEd^4$ where K is a constant determined by the thickness of the collimator, distance from the plane of observation, etc. Assuming for high count rates that $t_o \approx 2RC$ and that the desired resolution for the profile is $r = 4/d$, the expressions for the minimum observed fractional change for both systems may be shown to approximate

$$MOFC \cong \frac{4d^{-3}}{\left[\frac{KET_s}{A_s} \right]^{1/2}}$$

which reduces to $MOFC \cong d^{-3}/28$ for the case mentioned previously. This analysis shows a far more sensitive dependence on aperture size than on isotope concentration or scan time—indicating that one should use as large an aperture as possible for a given clinical problem. The above analysis assumes, of course, that the abnormality is larger than d^2 . Optimum sensitivity will be reached when the abnormality is equal to d^2 and decreases as the aperture is made larger. For very low counting rates (~ 8 cps), the influence of the RC weighting factor of the rate meter makes the above expression for $MOFC$ a factor of two larger

for profile presentation than for the visual storage.

Visual presentation in practice has several disadvantages that can be overcome by electronic techniques. One is the difficulty of assessing the absolute value of the data in depth and the other is the fact that for large abnormalities, the eye apparently uses the density gradient at the edge which results in an increase in minimum observable fractional change. This latter factor may be as high as 2 or 3 under unfavorable circumstances. However, minification (which increases the edge gradient), contrast enhancement and background erase may all be used to restore optimum detectability conditions. Likewise, proper electronic scanning of the image will produce a "profile" and, hence the data in depth, provided the visual record is related with a known and easily managed relationship to the original organ distribution.

It should be emphasized here that this analysis shows that the eye is capable of finding any defect observable in a profile on an untouched photoscan where the spatial density of spots is directly related to the detected counts. In actual practice, background erase is only used to detect abnormalities with greater ease. It does this by presenting only those signals larger than a given level. Because of the "soft" slope of the real resolution, this results in an apparent increase in sharpness and hence detectability. The same data can always be obtained in retrospect from the original scan. When the spots are overlapped such that film density is proportional to detected count, the film generally compresses the scale which then requires enhancement to bring it up to the original scale. Too much enhancement amplifies residual noise which then makes the analysis less certain.

It is perhaps important to note in passing that the scanners that use scalers to bring the detected pulse rate down to the speed of a "dot" recorder, a preset "erase" level (which has its own time constant) and which print out a narrow line for each scan line are really printing a visual representa-

tion of the count rate with a form of minification perpendicular to the scan lines. Some investigators have resorted to rotating the recording device 90 degrees and rescanning to improve apparent detectability in the other direction. A total storage device with adjustable minification would be much simpler.

SCANNING FRAME AND MOTIONS

The scanning system to be described here utilizes a commercially available frame,⁶ opposing collimator heads (over and under), and all the associated controls and meters to provide selectable areas (one line of any length to 2×6 foot scan areas); selectable scan speeds (3.5 inches/min. to 46.7 inches/min.) and selectable line spacings (1/16 inch to 1 3/16 inches).

Multi-turn potentiometers were added that produce D.C. signal levels proportional to position. These signals are fed to the positioning plates of an oscilloscope. A scale changing circuit is inserted between the positioning potentiometers and oscilloscope so that any size scan can be adjusted to just fill the recording area on the oscilloscope. The signals from the detecting crystal pre-amplifier pass through a pulse height discriminator to a special pulse shaping and spot brightening circuit for the intensity modulation of the oscilloscope. An ancillary count rate meter is provided for continuous monitoring as well as single point checks. The spot size on the oscilloscope is adjusted to approximate (or may be smaller than) the relative projected aperture size. This is not too critical an adjustment since, at the count rates generally encountered, any size spot will produce overlap and density addition on the film. Consideration of the data for a typical liver scan mentioned above shows that we store about 10^8 bits of information (counts). If such is placed uniformly (patently impossible for randomly occurring events) on a 3×2 inch oscilloscope pattern, we see that a spot size of about .005 inches is required for no overlap. Actually, a spot size of about .001 inch or less would be required in the practical case

and this is well beyond the limit of standard oscilloscopes. Thus, to produce a picture whose spatial density of spots would correspond to the signal (similar to newsprint photographs) one would have to go to much larger screens and much smaller spots. To date, we have preferred relatively large spots, spot overlap, and the subsequent use of transmission density.

Aesthetically, some people prefer a spot smaller than the projected aperture. We then defocus the television scan system to produce a picture similar to what the aperture actually "sees." This technique is to be preferred for still another reason: namely, that to adjust spot size for different ratios of aperture size to scan area is more difficult and time consuming than to always use a small spot and defocus the viewing television camera. Spot intensity is adjusted via a photocell viewer to produce the proper dynamic density range on the film and a special circuit is provided that will make spots containing any given preset number of counts for film calibration as well as position and distance calibrations. A polaroid oscilloscope camera is used that produces transparent negatives for television scans and positives for additional records. Figure 3 is a block diagram of the detecting and re-

cording system. The technique outlined above produces a film in a relatively short time (30 seconds after completion of the scan) that contains all the available information in a known form. It is an inexpensive and easily handled form of long-time total information storage.

DATA EXTRACTION SYSTEM

The system we use for analyzing the data on the film is a television replay system similar to that used by others¹ but with important modifications. First, we use uniform back illumination of the transparency, and view this with a vidicon camera. The output signal is then fed to a non-linear amplifier that has an adjustable low level cut-off (background erase) and a variable gain (contrast-enhancement). The output of this is finally fed to a slave kinescope that produces a picture as modified by the amplifier. At the same time, a line selector circuit chooses any given horizontal scan which is then presented as a one line profile or "slice" of the picture. An adjustable band width determines both the resolution of the picture and the effective RC time of the profile presentation. A line blanking circuit produces a black line on the kinescope picture that defines the position of the "slice."

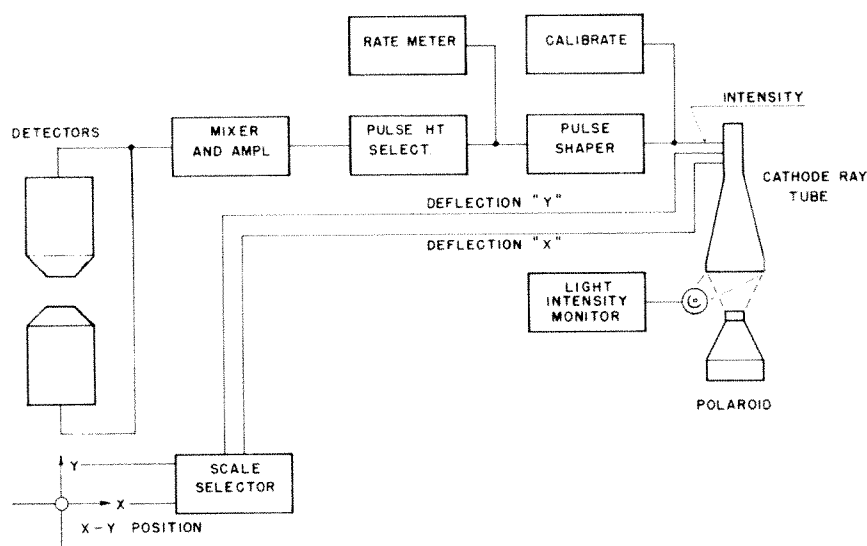


FIG. 3. Block diagram of detecting and recording system.

Simple rotation of the picture allows profiles to be made in any desired direction.

A word of caution is necessary against the use of too much contrast enhancement. Since enhancement is only increased amplification, all the noise in the original record, film, and vidicon is amplified as well as the desired signal. Thus, while such may produce a record of more "apparent" certainty (very black versus very white), the actual statistical uncertainties are increased even more and the true signal to noise ratio decreases. Contrast enhancement should only be used to the extent that the film compresses the original data.

Background erase does not do this and we have found that such a control coupled with a limited enhancement produces the best results.

Regarding band width, the considerations here are identical to those discussed previously for simple profile presentations with a count rate meter—the only difference being the time scales involved. Approximately 37 microseconds are required for one horizontal line scan and if one scan length corresponds to a 10 inch organ scan and we wish $\frac{1}{8}$ inch resolution to reproduce a $\frac{1}{2}$ inch projected collimator, then the circuit rise time becomes on the order of 0.5 microseconds. This is the time required for the signal to rise to 90 per cent of its final value for any sudden change. This corresponds to a nominal cut-off band width of 1 megacycle.

Most television systems have a much larger band width than this which in turn presents more statistical variations (noise) in the profile (and picture) than is necessary for the resolution. Hence the band width must be reduced to present smoother profiles and pictures.

Figure 4 is a graph illustrating the dependence of nominal band width on organ scan parameters, while Figure 5 is a block diagram of the over-all system. It is to be noted that an attachment has been added to the kinescope that will produce a variable minification of the image over a range of about 5 to 1. The value of this in aiding

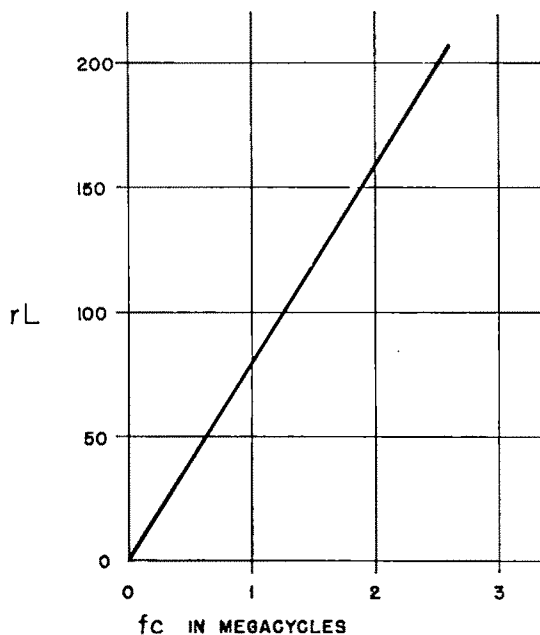


FIG. 4. Product of resolution ($r=4/d$) and scan length as a function of nominal band width.

detection of abnormalities has yet to be established.

It is to be noted that due to both film and vidicon characteristics, our profiles are not presented on a linear graph. This has been done with electro-optical feedback around a flying spot scanner,⁸ but the additional circuitry and optical elements made the system too complicated and expensive for the small increase in convenience. For our present system, it can be shown that the intensity of the light transmitted through the film is

$$I = I_0 N^{-\gamma} + \text{const.},$$

where $\gamma = 0.62$ and N is the number of overlapping events. For the polaroid film used, this holds over a dynamic range much larger than that encountered in scintiscanning. Likewise, the signal output of the vidicon for light intensity I is

$$S = 10^{0.7} I^{0.8} = \text{const.} N^{-1/2}$$

neglecting film background. Because of the inversion of black to white, the profile actually plots a voltage $V = C - KN^{-1/2}$. The constants are readily evaluated by use

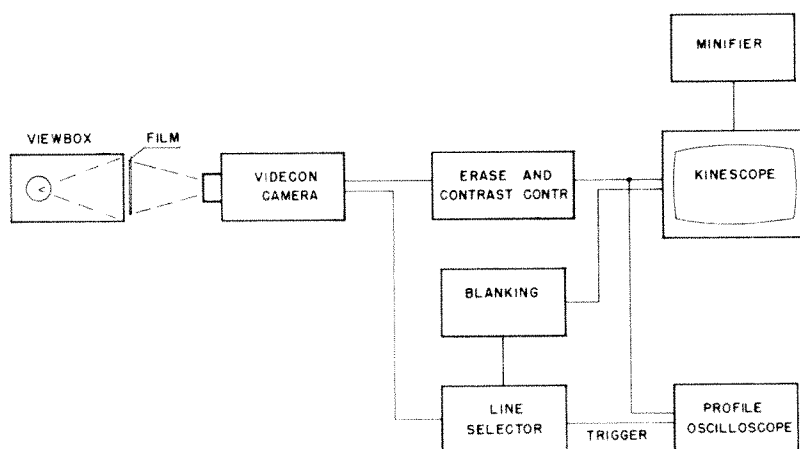


FIG. 5. Block diagram of enhancement, erase and profile system.

of the calibration spots on the original film. A rather interesting result is that if one of the spots has a very large number of events ($N \rightarrow \infty$), then the height of the profile for this spot determines an upper reference line from which measurements downward to the profile may be made. The length of this line is then a measure of the fractional standard deviation which for random events is $N^{-1/2}$.

The above relationship is plotted in Fig-

ure 6 where both V and N are in arbitrary units. Shown, too, is the influence of the enhancement and erase circuitry which demonstrates that increased contrast (enhancement) also multiplies any changes in N due to noise by the slope of the curve.

COLLIMATION

The type of collimation is obviously of importance in determining the operational performance of a scanning system. Since

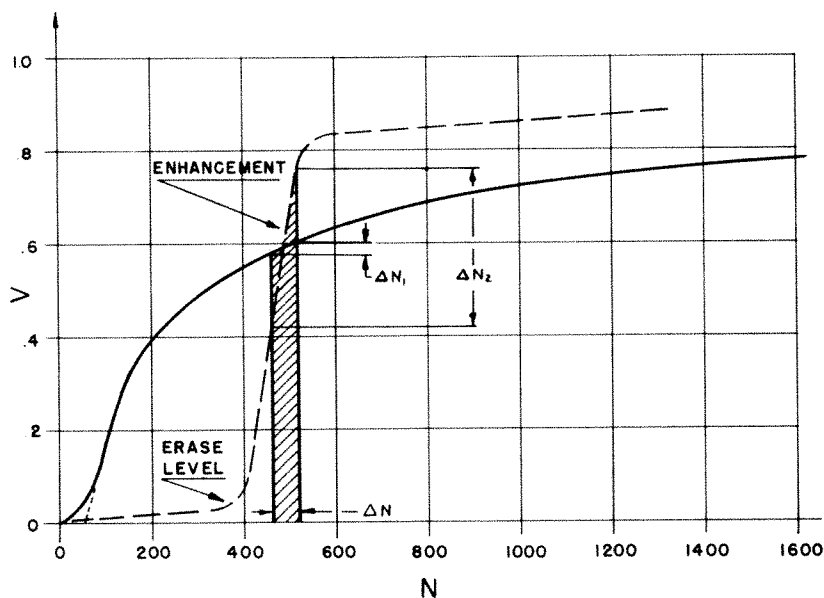


FIG. 6. The solid line is the relationship between vidicon output voltage and the number of overlapping events. The dotted line shows the effect on the transfer curve of a given erase level and enhancement. ΔN_1 and ΔN_2 are the normal and enhanced variations in output for a change of ΔN (i.e., noise fluctuations) in the input. All units are arbitrary.

few organs may be considered a planar distribution, the characteristics of the response in depth are of prime importance. Further, if the organ activity, scan time, and number of detectors are fixed, only a given amount of information is available and the observer must make a judgment as to the relative importance of resolution versus detectability of differences since increasing one decreases the other. It follows that at infinite resolution there is no detectability (*i.e.*, no signal), and, at increased detectability (high count rate due to a very large aperture), both the resolution and number of possible observable defects approach zero. Somewhere between the two is an optimum that the observer must establish, depending on his clinical criteria. Now all collimators have sources of signal other than those arising from the actual desired field of activity. These are leakage, scatter, and general background radiation. While scatter and some background can be minimized by pulse height selection and leakage by increased shielding, the residual noise establishes an upper limit to the resolution beyond which it is useless to attempt any measurements. For very "leaky" collimators, this may result in requiring a relatively large aperture.

Both experience and theory (to be published) indicate that for a reasonably shielded collimator (about 25 half-value layers), a projected aperture diameter of about $\frac{5}{8}$ inches will produce reasonably informative scans of a large organ (*i.e.*, liver or brain). It is to be emphasized that this choice will change with the size and shape of an organ, total activity and scan time available, and clinical criteria regarding the size of abnormalities of interest. For example, one would not consider using the above to scan a thyroid.

The type of collimator is also important. One has, in general, the choice of opposing versus single collimators with each collimator being straight bore, focussing with cylindrical holes and focussing with tapered holes. Opposing bores are advantageous in increasing the count rate by two when one wishes to observe the activity in

a cylinder through the volume. They are disadvantageous when other organs that also concentrate the isotope are in the line of detection. For example, when liver scanning, the spine and pelvis will show quite well with opposing collimators but will be almost absent when only one is used above the abdomen. In this case, however, such information could be of clinical value since the activity in the spine increases when liver uptake decreases due to disease.

Focussing collimators are simply an aggregate of straight bore collimators with a common point of intersection on a plane. While such is highly advantageous for a near planar distribution, it is not of particular advantage when analyzing a volume in depth. This is due to the fact that all the activity in the cone above and below the focal plane is added to the apparent signal (just like noise) and the physical location and size of any observed changes are difficult to ascertain. While they do produce higher counting rates, these are mostly due to extraneous and nonlocatable volumes that should be considered sources of "noise." A rather simple example of these statements is to consider a n -hole focussing collimator looking at a defect in one plane of a volume of activity. If the plane containing the defect is coincident with the plane of focus, then we have simply n straight bores seeing the same defect and, hence, should record a signal change n times what a single bore would see. Now, if the two planes are separated far enough, then we could have one straight bore seeing the defect and $n-1$ straight bores recording "noise." By "noise" is meant signal from volume activity possessing no information and which by its presence requires a much larger real change in the one bore to be observable. Thus, in this case, the result is far worse than a single bore by itself.

Actually, with a focussing collimator, one is sacrificing possible information about contrast for possible information about location in depth similar to laminagraphy in roentgenologic diagnosis. Obviously, in actual practice some compromise is made between the two extremes pictured above.

Because of (1) the very poor resolution for off-planar abnormalities, (2) influence of the integrated near and far observed volumes relative to the focal plane, and (3) the lack of sharp edges on most physiologic abnormalities, it is our feeling that for scanning volumes (a) tapered holes are unnecessary, (b) planar response curves are not a sufficient indication of the value of a particular collimator design, and (c) little if anything is gained in having too many holes and large crystals.

For the same size of projected aperture, we have found little if any difference in the ability to detect and specify abnormalities in a large volume between focussing and single bore collimators. Our scanner has opposing 2 inch by 2 inch crystal detectors with which either focussing or straight bore collimators can be used. For kidneys, and sometimes liver scans, use was made of only the upper unit. In the examples that follow only focussing collimators were employed.

CLINICAL RESULTS

Figures 7 through 14 inclusive are typical clinical results selected to demonstrate the usefulness of the technique described here. While the value of the profile is obvious, many of the clinical diagnoses would not have been possible—or at least would have been extremely difficult and time consum-

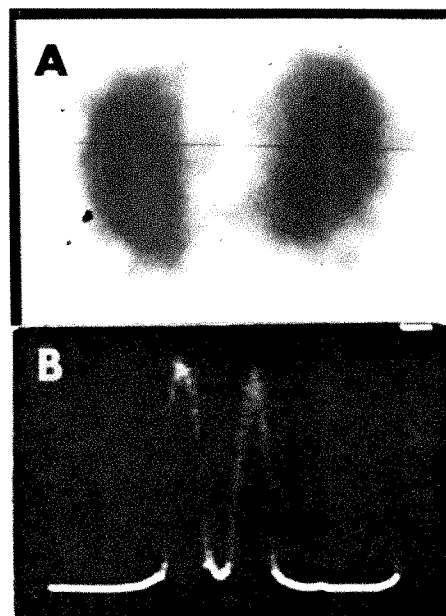


FIG. 8. (*A* and *B*) Normal renal scan and profile through the center of both kidneys. This scan made with 250 μ c of Hg^{197} tagged chlormer and one 19 hole focussing collimator.

ing—with more conventional scanning systems not possessing the capability to idly and continuously adjust the ϵ and contrast for optimum detection.

Figures 7, *A* and *B*, and 8, *A* and *B* demonstrate the profiles obtained for normal liver and kidney scans. It is important to note that these profiles do not measure "uptake" but rather the activity as

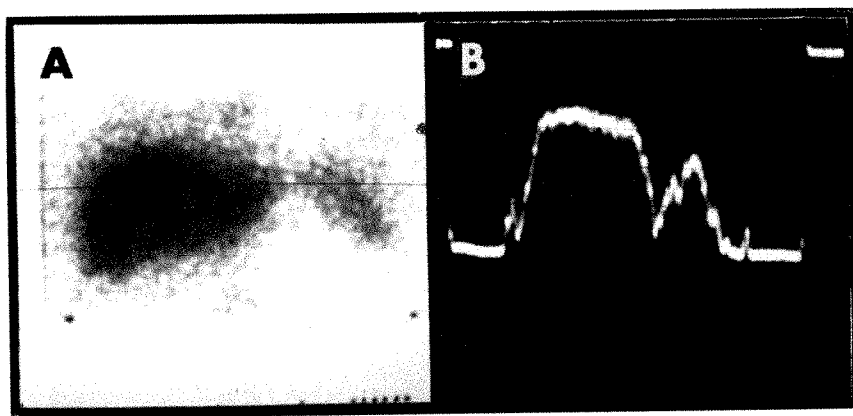


FIG. 7. (*A* and *B*) Normal hepatoscan without erase and profile through midline. This scan was made with 300 μ c of Au^{198} and two opposing 19 hole focussing collimators.

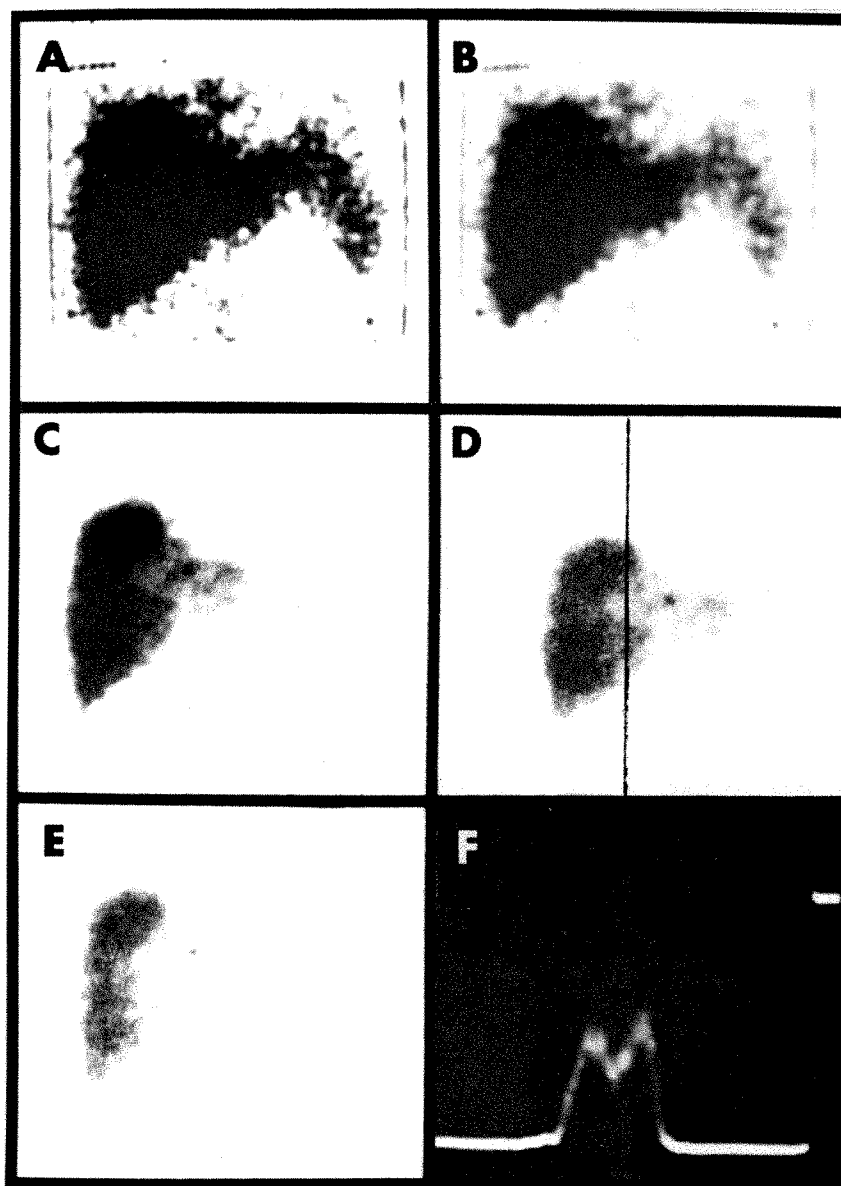


FIG. 9. (A-F) Hepatoscan showing successive erase levels which ultimately demonstrate a space occupying lesion. Profile is shown for a vertical "slice" through the organ. This is accomplished by simply rotating the original picture on the viewbox. Scan conditions same as in Figure 7.

(Reference on following page)

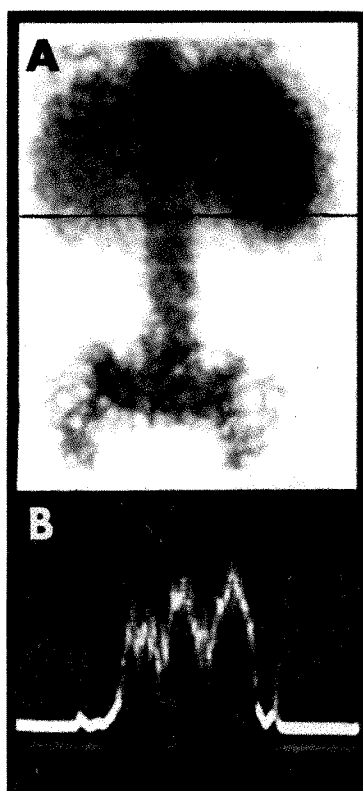


FIG. 10. (*A* and *B*) Hepatoscan with partial erase and midline profile showing increased spleen and marrow uptake due to disturbance of liver function and/or circulation. Scan conditions same as in Figure 7.

and geometrically defined by the collimator. "Uptake" would be the integral of successive profiles over the whole organ. In Figure 9, *A-F* the effect of successive erase levels in enhancing an abnormality is seen. In this case, exploratory laparotomy revealed metastatic adenocarcinoma at the porta hepatis but no evidence of a space occupying lesion in the liver. An autopsy 2 weeks later revealed a large necrotic mass, 8 cm. in diameter, in the right lobe. Figure 10, *A* and *B* is a hepatoscan of a patient with a history of alcoholism of 30 years' duration. Study of the profile showed that the patchiness of the liver was much greater than the expected statistical variations and was probably due to fibrotic changes. The same profile shows the abnormal uptake of colloidal gold in the bone marrow and the greatly enlarged spleen.

Figure 11, *A* and *B* is a renal scan of a patient admitted because of a grand mal seizure and hypertension of 4 years' duration. While it is obvious that one kidney is not concentrating any chlormerodrin, the other kidney appears somewhat normal when the liver and high background are removed.

Figure 12, *A* and *B* is a renal scan of a patient who had known congestive heart failure, fibrillation and cardiomegaly of 6 years' duration and who was admitted for sudden and persistent pain above the right sacroiliac joint. With proper erase conditions, a large defect in the upper pole of the right kidney was obvious. This was consistent with the clinical impression of embolism to a segment of the right kidney.

Figure 13 is a cardiac scan of a patient admitted because of a complaint of progressive dysphasia and an enlarged non-tender swelling in the lower part of the neck. While an aneurysm was suspected,

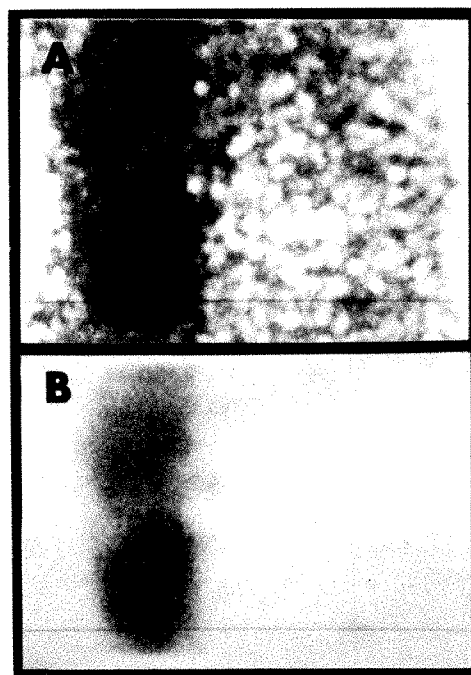
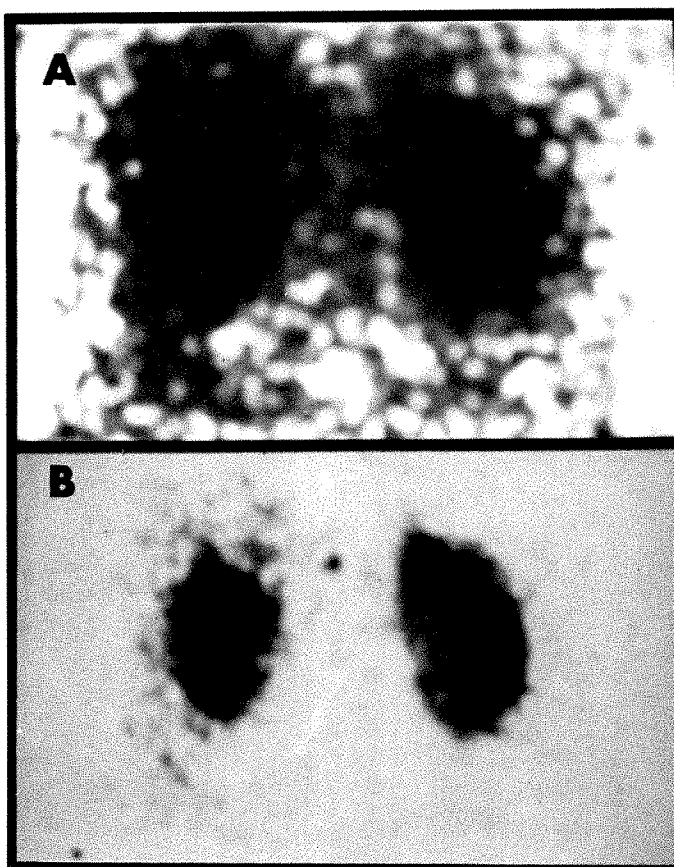


FIG. 11. (*A* and *B*) Renal scan showing an increased uptake of Hg^{197} tagged chlormerodrin in the liver, a normal right kidney, and a very low uptake in the area of left kidney. Scan conditions same as in Figure 8.

FIG. 12. (*A* and *B*) Kidney scans without and with background erase. The right kidney measured about 8 cm. in length while the left measured 10 cm., the difference being due to an apparent infarct in the upper pole of the right kidney. Scan conditions same as in Figure 8.



two attempts at cineangiocardiology and one at retrograde aortography were unsuccessful. The properly erased scan suppressed the adjoining pulmonary vascular pools and made clear the distortion of the aorta and large vessel pools as shown. This

permitted the diagnosis of a possible aneurysm of the right innominate and subclavian artery which was found and resected at surgery.

Figure 14, *A* and *B* is a routine brain scan performed on a patient who was ad-

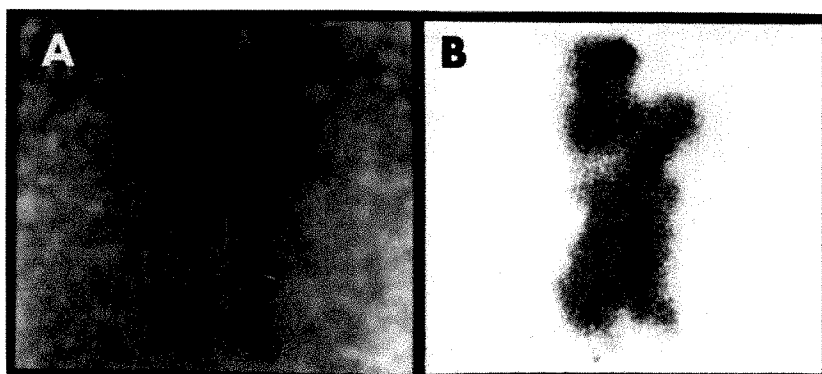


FIG. 13. (*A* and *B*) Cardiac scan using RISA and one focussing collimator on a patient with a suspected aneurysm of the great vessels and substernal thyroid.

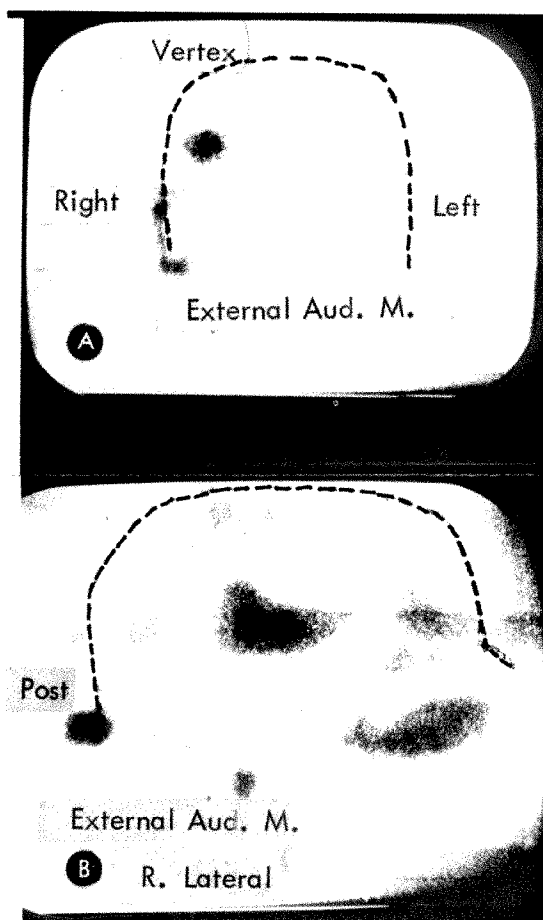


FIG. 14. (A and B) Brain scan with erase and enhancement performed with a 91 hole focussing collimator 4 to 5 hours after the intravenous administration of 1 mc of Hg^{197} tagged chlormerodrin.

mitted because of a vague pressure headache of 6 months' duration. An abnormal

concentration of chlormerodrin in the right temporoparietal region was seen on an erase scan and a subsequent craniotomy revealed glioblastoma in the same region.

SUMMARY

A system for radioisotope scanning by which all information received by the detector can be stored and later extracted is described. Ancillary devices are used for enhancement of the visual detection of abnormalities.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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EDITORIALS

THE r AND c UNITS

SINCE the discovery of x rays in 1895 and of radium in 1898, various methods have been tried for specifying the dose used in medical application. Such methods were based on the photographic, fluorescent, chemical and certain biologic effects of the roentgen rays and radium. After two decades of investigative efforts, it became evident that an ionization method, already proposed by Villard in 1908, carried the greatest promise.

The history of the r unit. The roentgen (r) unit, based on ionization of air, has a rather intricate, but fascinating, history.

In the early 1920s, several electrostatic methods based on ionization of air were devised, expressing the intensity of a beam of roentgen rays in some unit of measurement. In the United States, Duane¹ proposed the E unit which was defined as the unit of intensity of a beam of x rays that would produce an ionization current of 1 esu in each cc. of air if the rays did not strike any of the electrodes in the ionization chamber, and if all of the secondary radiation from the molecules of the air were absorbed in the air.

In Germany, as a result of numerous investigations, among several units proposed, the Behnken unit,² designated by the symbol of capital R, found widest acceptance and in May, 1924, was adopted by the German Roentgen Society as the official unit. It was defined as a unit of roentgen-ray dosage, being that quantity which when applied to 1 cc. of air at 18° C. and 760 mm. Hg of pressure engenders sufficient electric conductivity to equal 1 esu, as measured by the saturation current.

In 1925, Solomon^{3,4} presented to the First International Congress of Radiology in London, an electrostatic unit based on a different type of measurement which also was designated by the symbol of capital R. This unit was defined as the intensity of a roentgen-ray beam producing the same ionization as 1 gram of radium element, placed at a distance of 2 cm. from the ionization chamber, axis to axis, and filtered by 0.5 mm. Pt.

There was also the R unit, used in Cleveland by Glasser, which was measured by an air wall thimble ionization chamber.

The years following the First International Congress of Radiology were characterized by laborious work aiming to reach international agreement on the standardization of these various electrostatic units. Glasser visited several institutions in Europe and in 1927 Behnken brought to America several dosimeters especially constructed for comparative measurement of the units. With these instruments the German R unit was compared with the E unit used by Duane in Cambridge, Massachusetts, and the R unit used by Glasser at the Cleveland Clinic. The measurements did not give any difference of practical importance between the units.^{5,6} Glasser, by using the condenser dosimeter constructed by him and Seitz in 1928,⁷ also found that, when the distance in the Solomon measurements was reduced from 2 cm. to 1.54 cm., the Solomon R assumed a value identical

³ SOLOMON, I. Sur le choix d'une unité quantimétrique internationale. *J. de radiol. et d'électrol.*, 1926, 10, 155-158.

⁴ SOLOMON, I. Les unités quantimétriques en roentgentherapie. *J. de radiol. et d'électrol.*, 1924, 8, 351-356.

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⁶ BEHNKEN, H., and JAEGER, R. The standardization of x-ray dosage. *Radiology*, 1928, 10, 273-279.

⁷ GLASSER, O., QUIMBY, E. H., TAYLOR, L. S., WEATHERWAX, J. L., and MORGAN, R. H. *Physical Foundations of Radiology*. Third edition. Paul B. Hoeber, Inc., New York, 1961.

¹ DUANE, W. The scientific basis of short wave-length therapy. Third Caldwell Lecture. *AM. J. ROENTGENOL.*, 1922, 9, 781-791.

² BEHNKEN, H. Die Röntgendosimetrie. In: *Handbuch der gesamten Strahlenheilkunde, Biologie, Pathologie und Therapie*. Bergmann Verlag, München, 1929.

to that of the Cleveland R.⁸ This condenser type of dosimeter⁹ has become known as the Victoreen condenser r-meter and is one of the most generally used instruments in medical application of radiation today.

As a result of these co-ordinating efforts, the International X-ray Unit Committee made at the Second International Congress of Radiology in Stockholm (1928) the following proposals¹⁰ which were provisionally accepted: (1) That an international unit of x-radiation be adopted; (2) that this international unit be the quantity of x-radiation which, when the secondary electrons are fully utilized and the wall effect of the chamber is avoided, produces in 1 cc. of atmospheric air at 0° C. and 76 cm. mercury pressure, such a degree of conductivity that 1 esu of charge is measured at saturation current; (3) that the international unit of x-radiation be called "The Röntgen" and that it be designated by the letter small "r."

Following acceptance of the r as the international unit, the extremely difficult task of devising and constructing suitable instruments to measure it in a standardized form began. The many contributions by Taylor and his associates at the National Bureau of Standards, Washington, D. C., were of immeasurable help in this respect.⁷ In 1930 Taylor developed an American standard air ionization chamber for the precise measurement of the r^{11,12,13} and in the summer of 1931 he transported a smaller guarded field ionization chamber developed in his laboratory to Europe. With this sufficiently compact instrument, preliminary standardization was made in Washington, then measurements were carried out in Teddington, England (National Physical

Laboratory), Berlin, Germany (Physikalisch-Technische Reichsanstalt), and Paris, France (L'Hôpital St. Antoine), and at the end the results were compared with the original standard in Washington. These results were presented in a report at the Third International Congress of Radiology in Paris (1931) and published in final form in 1932.¹⁴

The Fifth International Congress of Radiology in Chicago (1937), in view of the fact that the r unit was also extended to radium, adopted a somewhat more generalized definition of the roentgen.¹⁵ It was as follows: (1) The international unit of quantity or dose of x rays or gamma rays shall be called "roentgen" and shall be designated by the symbol "r." (2) The roentgen shall be the quantity of x- or gamma radiation such that the associated corpuscular emission per 0.001293 gram of air produces, in air, ions carrying 1 esu of quantity of electricity of either sign. In an Appendix it was specified that 0.001293 gram is the mass of 1 cc. of dry atmospheric air at 0° C. and 760 mm. of mercury pressure. (3) Measurements of radiation quantity shall be expressed in roentgens, and measurements of dosage rate shall be expressed in roentgens per minute.

At the Sixth International Congress of Radiology in London (1950),¹⁶ in an endeavor to correlate the dose of any ionizing radiation with its biologic or related effect, the International Commission on Radiological Units (ICRU) recommended that the dose be expressed in terms of the quantity of energy absorbed per unit mass (ergs per gram) of irradiated material at the place of interest. As regards the roentgen it stated that the Commission considers that the roentgen (designated by the symbol r), in view of its long established usefulness, should continue to be recognized as the unit of x- and gamma-ray quantity or dose and that its definition remain unchanged.

⁸ GLASSER, O., and SEITZ, V. B. La valeur des unités R pour la standardization de la dose dans la pratique radiologique. *J. de radiol. et d'électrol.*, 1928, 12, 421-428.

⁹ GLASSER, O., and SEITZ, V. B. Method and apparatus for the measurement of radiation intensity. U. S. Patent 1,855,669. April 26, 1932.

¹⁰ Report from the International X-Ray Unit Committee. *Am. J. ROENTGENOL. & RAD. THERAPY*, 1928, 20, 470-471.

¹¹ TAYLOR, L. S. The precise measurement of x-ray dosage. *Radiology*, 1930, 14, 372-384.

¹² TAYLOR, L. S., and SINGER, G. An improved form of standard ionization chamber. *Radiology*, 1930, 15, 637-646.

¹³ TAYLOR, L. S. Recent progress in x-ray standardization. *Radiology*, 1931, 16, 1-13.

¹⁴ TAYLOR, L. S. International comparison of x-ray standards. *Radiology*, 1932, 18, 99-114.

¹⁵ Recommendations of the International Committee for Radiological Units (Chicago, 1937). *Radiology*, 1937, 29, 634-636.

¹⁶ Recommendations of the International Commission on Radiological Units (London, 1950). *Radiology*, 1951, 56, 117-119.

The Seventh International Congress of Radiology in Copenhagen (1953),¹⁷ adopted the rad as a unit of "absorbed dose" of any ionizing radiation, equal to 100 ergs per gram of any absorber. The unit of the quantity of radiation delivered to a certain place, called the "exposure dose," remained the roentgen (r). It was specified that this unit may be used for most practical purposes for quantum energies up to 3 mev.

The history of the c unit. The curie (c) unit has a history which dates back to the very early days of the use of emanation in clinical therapy. Pierre Curie¹⁸ in 1904 expressed the quantity of emanation in milligram hours and defined it as the quantity of emanation produced in 1 hour by 1 milligram of radium element. In 1909 Turner¹⁹ was apparently the first to use the term milligram hour (mg. hr.) for specification of the dosage in radium therapy, and in 1910 the curie was adopted as the unit of measurement for the emanation. One mc, or 1/1000th curie, was defined as the quantity of emanation in equilibrium with 1 mg. of radium elements. Following some changes in the basic approach of dosage, within a short time 3 units¹⁸ became of common usage: the mg. hr. for the radium; the mc hr. for the emanation present; and the mcδ for the emanation destroyed (1 mcδ representing 133 mc hr.). These units are still valid today, although the mcδ is now less frequently employed.

After the adoption of the international r unit for roentgen rays and, in particular, with the advent of radioactive isotopes, efforts were made to extend the same unit also to the measurement of the gamma rays of radium, radon and other members of the naturally radioactive families, as well as to the many radioactive isotopes used. Glasser and Portmann,²⁰ who contributed

so greatly to the unification of the different roentgen units, in 1928 made the statement "that the r unit may be used with a great degree of accuracy for the dosage unit of both roentgen and radium therapy."

At the Fifth International Congress of Radiology in Chicago (1937),¹⁵ pursuant to the recommendations in reference to gamma-ray dosage made at the Fourth Congress in Zurich (1934), it was adopted—as already stated—that the roentgen also be the international unit for the measurement of the quantity or dose of the gamma rays and shall be designated by the symbol r. Finally, at the Sixth International Congress of Radiology in London (1950),¹⁶ the ICRU recommended that the curie be used for the measurement of any radioactive material, being a unit of radioactivity defined as the quantity of any radioactive nuclide in which the number of disintegrations per second is 3.7×10^{10} . Furthermore, it was suggested that the gamma-ray emission be expressed in terms of r/mc hr. at 1 cm. from a point source. This definition of curie was officially adopted at the Seventh International Congress of Radiology in Copenhagen (1953).

Usage. In the 1956 Report of ICRU²¹ in regard to the usage of symbols and nomenclature, it was recommended that each country modify them in accordance with its own practices. Thus one may write: kev., keV., or Kev.; ¹⁴C or C¹⁴; rad per unit time, rad per time, or rad divided by time; rad/sec., rad/s, or rad.s⁻¹, etc. Concerning the r and c units, the statement was made that the unit of exposure dose of x- or gamma radiation is the roentgen (r); and the unit of quantity of radioactive material, evaluated according to its radioactivity, is the curie (c).

Then, following the report of an *ad hoc* Committee set up in 1959 for the purpose of re-examining the whole problem of radiation quantities and units and as a re-

unit for the measurement of roentgen and radium radiation. *Radiology*, 1929, 12, 317-327.

²¹ Report of the International Commission of Radiological Units and Measurements (ICRU) 1956. National Bureau of Standards Handbook 62.

¹⁷ Recommendations of the International Commission on Radiological Units; Revised at the Seventh International Congress of Radiology, Copenhagen, July, 1953. Editorial. *Radiology*, 1954, 62, 106-109.

¹⁸ REGAUD, CL., and FERROUX, R. Doses et durée d'application en radiumthérapie; procédés de notation et de calcul; table pour l'emploi de l'émanation du radium. *J. de radiol. et d'électrol.*, 1918-1919, 3, 481-507.

¹⁹ TURNER, D. The effect and use of radium. *Lancet*, 1909, Dec. 25, p. 1875.

²⁰ GLASSER, O., and PORTMANN, U. V. The reliability of the r-

sult of much consultation with various standardization task groups, the ICRU in 1962 made certain new recommendations.²² Since the "absorbed dose" is the physical quantity which can be most closely correlated with biologic effects, the designation of this quantity was maintained, but, for designation of the quantity of x- and gamma radiation of which the roentgen is the unit, it was recommended that the word "dose" be eliminated from "exposure dose" and the term "exposure" be used alone. Also, the curie has been redefined as $3.7 \times 10^{10} \text{ s}^{-1}$, *i.e.*, as a unit of activity and not of quantity of a nuclide. Most important from the point of view of established usage, however, is the fact that it also recommended that since "several recognized international groups working in the field of symbols and nomenclature including the International Council of Scientific Unions have agreed upon the convention that the first letter of abbreviations of units named after individuals should be capitalized," this also be applied to the r and c units. Thus, the use of the symbol R instead of r was proposed for the roentgen unit and in 1963²³ the symbol Ci instead of c was adopted for the curie unit. Based on these new symbols such commonly used abbreviations as mr, rep, rem, and rhm would be replaced by mR, Rep, Rem, Rhm and mc hr., r/mc hr., $\mu\text{C/gm.}$ by mCi hr., R/mCi hr., $\mu\text{Ci/g.}$, etc.

Style of the "JOURNAL." The term "style" usually refers to forms of expression and details of typography, as for instance, spelling and capitalization of words, use and capitalization of symbols, use of punctuations, division of words, etc. Often, because of long continued usage, certain words and symbols become ingrained in a sense not always intended and are difficult to change.

The style of the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY &

NUCLEAR MEDICINE was based from the beginning on two fundamental principles.

In articles dealing with subjects of the allied fields, such as pure physics, engineering, physical chemistry, radiobiology, optics, photography and especially pharmacology, the nomenclature and symbols were used as developed in each particular field.

In the domain of medical radiology, as a result of a practice initiated in 1912, and consistently followed since then, a style has been built which has become a characteristic feature of the JOURNAL. In referring to certain facets of this style, Etter, in 1963, in an Editorial titled "The Language of Radiology" aptly re-emphasized the significance of this style to the radiologist.²⁴

As regards the usage of the r and c symbols, the JOURNAL always observed the recommendations made by the ICRU and various other organizations, as outlined above. It would be difficult today to find symbols of 2 other physical units which have acquired such universal acceptance not only in the radiologic literature but the medical literature in general as the r and c symbols. Even in the medical use of g., which is one of the three fundamental pillars of the cgs system, a compromise had to be made, gm. being used for gram and gr. for grain, and there are other examples.

In Handbook 84,²² issued November 14, 1962, it is stated that the ICRU recommends the change "with considerable reluctance and some misgivings," and that "as far as medical radiology is concerned, this change will result more in annoyance than confusion." In the case of the JOURNAL, to remain consistent with the application of the new rule of capitalization to all other symbols appearing on its pages, it would mean the necessity of a very definite change in its long-established style.

T. LEUCUTIA, M.D.

²² National Bureau of Standards Handbook 84. (Issued November 14, 1962.)

²³ National Bureau of Standards Handbook 86. (November 1963).

²⁴ ETTER, L. E. The language of radiology. Editorial. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1963, 90, 656-658.



OTTO GLASSER, PH.D.
1895-1964

DR. OTTO GLASSER, emeritus consultant to the Department of Biophysics at the Cleveland Clinic, died in Cleveland Clinic Hospital on December 11, 1964 after a long illness. He was one of this country's outstanding authorities and early pioneers in radiology, radium therapy and nuclear medicine.

Dr. Glasser was born in Saarbruecken, Germany, in 1895 and served in the First World War, was severely wounded after 6 months of duty and was awarded the Iron Cross. He was educated at the Universities of Freiburg and Heidelberg. He came to this country in 1922 and joined the Cleveland Clinic the next year. He taught at the

New York Postgraduate Medical School and Hospital (Columbia) in 1926-1927 and then returned to the Clinic as head of its Department of Biophysics. He became an emeritus consultant in 1960.

Dr. Glasser received many honors for his work, both in this country and abroad. He wrote the definitive biography of Röntgen and was the only American given a diploma and medal commemorating the 50th anniversary of the first Nobel Prize in Physics awarded to Wilhelm Conrad Röntgen. He built one of the first x-ray dosimeters and his original model is now in the Smithsonian Institute.

Dr. Glasser was the author of more than 150 scientific papers. He also compiled and edited the monumental 3 Volumes on Medical Physics.

Dr. Glasser was an Honorary Member of the American Roentgen Ray Society and of the Ohio State Radiological Society and was awarded the Janeway Medal of the American Radium Society in 1950. He won a special Certificate of Honor for his roentgen exhibit at the American Medical Association Meeting in 1930, the Gold Medal Achievement Award of the Radiological Society of North America, the Olympia Decoration, the John Stanley Coulter Plaque, the American Congress of Physical Medicine Medal and was made Commander of the Cross Order of Merit by the German Government in 1960.

He was a Diplomate of the American Board of Radiology and a member of the AAAS, the American College of Radiology, the American Physics Society and held honorary membership in many societies here and abroad.

Dr. Glasser was a member and Subcommittee Chairman of the Committee on Standards of X-ray Measurement of the Radiological Society of North America; consultant in biophysics to Western Reserve University; special examiner of the American Board of Radiology since 1936; consultant on radiology to the U. S. Veterans Administration; member of the scien-

tific committee of the Ohio Post-war Program Commission; member of the Council on Physical Medicine and Rehabilitation and also of the Council on Medical Physics of the American Medical Association; member of the Control and Regulation Committee of the Governor's Advisory Council on Atomic Energy, and of the Ohio State Radioactive Advisory Council.

In 1961 the Ohio State Radiological Society inaugurated the Otto Glasser Award in his honor.

Dr. Glasser was one of the earliest to measure radioactive fallout. He did this by melting snow and reducing it to its powdery sediment and testing it. From this he not only could measure the fallout but could tell what the atomic bomb was made of before this ever was made public.

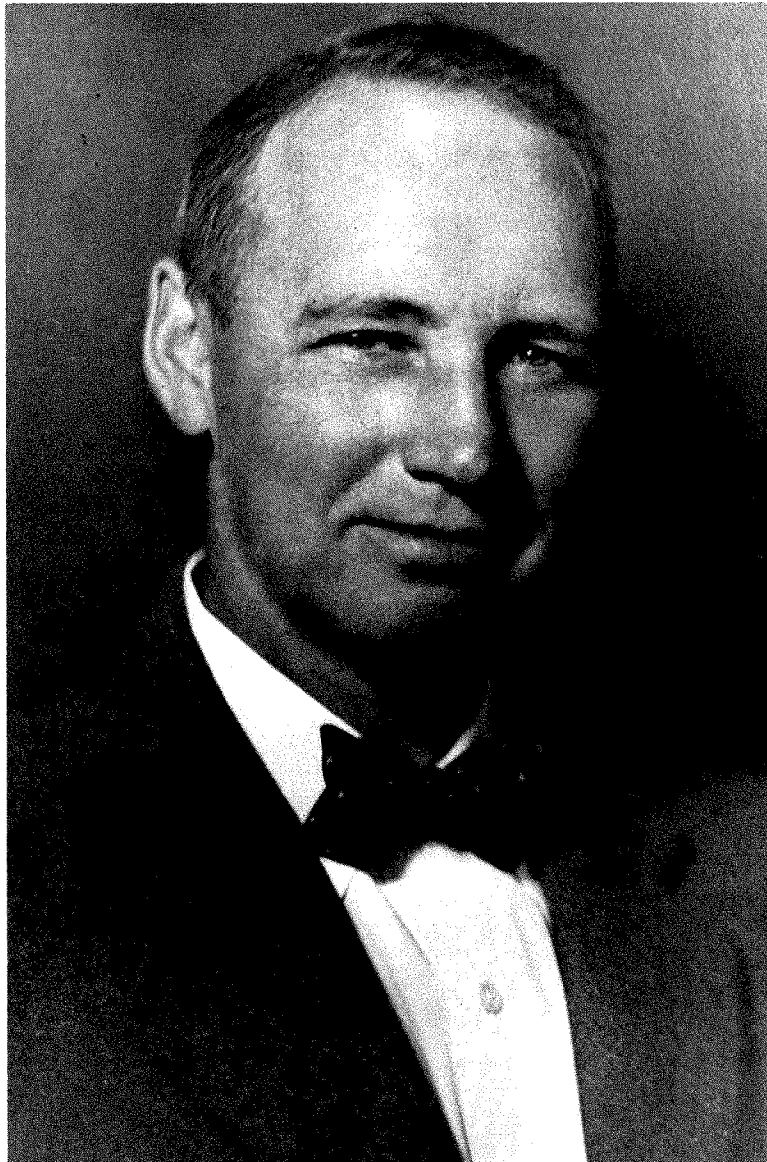
He pioneered in the x-ray diffraction of kidney stones and was one of the first to show the radioautograph of tissue sections. With Dr. Irvine H. Page of the Cleveland Clinic, he did notable work on hemorrhagic shock and arterial transfusions. He was one of the first to work in aviation medicine. With the late Dr. George Crile, Sr., early in World War II, he simulated the "bends," using animals to test physiologic results and treatment. They also demonstrated the potential gradients of electric current in various human organs.

During World War II he calibrated many million volt machines for the government in arsenals and munition plants, as he had earlier calibrated many medical x-ray units all over the nation. He was one of the early users of radioactive isotopes and helped standardize them and fix their terminology for the AEC.

Dr. Glasser is survived by his wife, Emmy, and a daughter, Hannelore, an Assistant in the Art Department of Wells College, Aurora, New York.

DON DUNHAM

The Cleveland Clinic
Cleveland, Ohio 44106



E. A. ADDINGTON, M.D.
1906-1964

DR. ERCEL A. ADDINGTON, Seattle, Washington, Radiologist and Vice President of the Board of Regents of the University of Washington, died on October 1, 1964 while vacationing in Lisbon, Portugal. He was 58 years old. His death was due to coronary occlusion complicated by pneumonia.

Dr. Addington was born in Algoma, Wisconsin. He attended high school in St. Croix, Wisconsin. He graduated from Carleton College in 1928 with a B.A. degree. He attended the medical school at the University of Minnesota and graduated in 1932 with an M.D. degree (he also received a B.S. degree in 1931 for his work done at the

medical school). He interned at the Santa Clara Hospital, San Jose, California, in 1931 and 1932. He then went into general practice in Dressler and later in Ellsworth, Wisconsin. He entered the Mayo Foundation of the Graduate School of the University of Minnesota, January 1937, as a Fellow in Radiology at the Mayo Clinic. He completed his Fellowship in October 1939 and received the degree of Master of Science in Radiology from the Graduate School of the University of Minnesota in December, 1940.

Dr. Addington married Mary Alice Kirstad in 1930 while in Medical School and leaves, besides his widow, a son, a daughter and one granddaughter.

These dry facts fail entirely to describe Ercel Addington as a personality: affable, cheerful, a good listener as well as a good talker; he was a stranger to no one within a few minutes. He could enter a room with a group of people and in a short time was the center of some interesting and frequently profitable discussion. He knew the people he met and could remember their names. He was diplomatic in his associations with others without being subservient. In spite of all the attributes of a good politician, he never went into medical politics. As a radiologist he was appreciated and respected by his associates and by the referring physicians. His ability to get along with the administration of Providence Hospital of Seattle, of which he was a Radiologist, contributed much to the smooth running of the department at the hospital in spite of a heavy radiological load and over-crowded quarters.

Ercel Addington's ability to make friends and to be truly interested in his fellowmen may relate to the early small town upbringing. As a student and athlete he was outstanding. As an undergraduate at Carleton, Erc was an outstanding player in three sports: football, basketball and baseball. In 1925 he received a gold football as a member of Carleton's midwest conference championship eleven. In baseball, he distinguished himself as a pitcher and in basketball as a forward.

He earned his way through medical school playing semiprofessional baseball and, when offered a contract by one of the major league baseball teams, had to decide whether to go into professional baseball or continue medicine. Luckily, he chose the latter. During his Fellowship at the Mayo Clinic, he was an outstanding student and, according to the other Fellows in Radiology there at the same time, he was also considered to be the leader of the group.

On completing his Fellowship, he came to Spokane, Washington, to become associated with a group of Radiologists having offices in Spokane and Seattle. At the start of World War II, when one partner was already in the service, Erc voluntarily accepted a commission as a Captain in the Medical Corps of the Army, in spite of his training and experience. He was very much disturbed at the prospect of being declared essential and being kept out of the war. He left the service as a Major at the end of World War II. On returning to civilian life, he wished to practice in Seattle and accordingly took over as a Senior Radiologist of the Seattle Group. He was an immediate success and was primarily instrumental in developing the diagnostic side of Radiology for the group in Seattle. He remained a general Radiologist with about one-third of his time being contributed very competently to Therapeutic Radiology.

Dr. Addington was closely associated with the Medical School of the University of Washington and for years was Clinical Assistant Professor of Radiology.

His crowning achievement was that of being appointed to an unexpired term of Regent of the University of Washington in 1961. In 1963 he was appointed to a full term as Regent and was elected Vice President of the Board. He fully recognized and accepted the obligations going with the honor of the appointment, knowing that the position added greatly to his work load and knowing also that he had been receiving warnings relative to his heart condition as far back as 1953. He was untiring in his efforts with the Board of Regents and con-

tributed a great deal during the short period of time that he was a member of the Board.

Dr. Addington's death leaves a great void in the practice of Radiology in the

Pacific Northwest and particularly with his former associates and other friends.

MILO T. HARRIS, M.D.

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Spokane 1, Washington



CONSIDERATIONS IN THE HANDLING OF RADIUM SOURCES

SUMMARY OF CONFERENCE ON RADIUM AND RADIUM SUBSTITUTES

(September 3-4, 1964, Chicago, Illinois)

By WENDELL G. SCOTT, M.D., ST. LOUIS, MISSOURI, and
JOHN C. VILLFORTH, M.S., WASHINGTON, D. C.

SINCE 1961 eight states have assumed licensing and regulatory powers from the Atomic Energy Commission over "by-product, source and special nuclear material" under an act passed by Congress in 1959. This law accelerated development in the states of radiation control programs to encompass all forms of ionizing radiation. This would include radium which has played a major role in medical practice.

A recommendation of the National Advisory Committee on Radiation (NACOR) was to investigate the practicality and means by which less hazardous, but equally effective, radioactive materials can be utilized in medicine. Acting upon this recommendation, the Division of Radiological Health of the United States Public Health Service sponsored a conference for the mutual exchange of information on radium and radium substitutes with members of the medical profession. Those invited to participate were representatives from the appropriate medical societies, and prominent therapeutic centers, as well as interested parties in the Atomic Energy Commission.

The Division of Radiological Health presented a summary of its radium studies, which included information obtained from a review of past radium incidents and accidents and experience of State Health Agencies with radium health problems. The participants were then encouraged to comment on the material presented based on their own personal experiences, and propose possible solutions.

The conclusions formulated by this conference were accepted unanimously by the participants. They will serve as valuable

guidelines in radium management for the medical profession, state and local health departments and to the Public Health Service.

These conclusions are as follows:

1. All naturally occurring radionuclides, including radium, radon, mesothorium, etc., as well as accelerator-produced radionuclides, should be subject to the same radiation protection regulations as are reactor-produced radionuclides.

2. Because of the special contamination hazards associated with radium, due to its physical and chemical properties, minimum standards of source design, construction and testing should be established for this radionuclide by a body of appropriate experts.

3. A suitable substitute for radium, with less contamination hazard, is desirable. Because of the large body of clinical experience accumulated with radium, substitute sources should be made available which conform to the dimensions and dose distribution patterns of existing radium sources. Cesium 137 sources seem capable of satisfying these requirements. For temporary interstitial treatments, where flexibility and shielding are an important consideration, iridium 192 is the isotope of choice at the present time. For permanent implantation, gold 198 is a suitable substitute for radon. The use of radium plaques should be discontinued; strontium 90 plaques are a suitable substitute.

4. It is further recommended that research be directed to the development of better radiation sources for brachytherapy. The possibility of fabricating better and safer sources employing presently used

radionuclides, including radium, should be considered.

5. The development of new techniques, such as after-loading techniques, to reduce unnecessary personnel exposure in the therapeutic applications of radionuclides should be supported and encouraged.

The following is a list of the participants of the Conference and the organizations they represented:

Axel Arneson, M.D., Professor of Clinical Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri—American Gynecological Society.

Arnold Berman, M.S., U. S. Atomic Energy Commission, Division of Isotopes Development, Germantown, Maryland—U. S. Atomic Energy Commission.

Harry L. Berman, M.D., Chief, Radiotherapy Section, Sinai Hospital of Baltimore, Baltimore, Maryland—American Roentgen Ray Society.

John Boland, M.D., Radiotherapist-in-Chief, Mt. Sinai Hospital, New York, New York—Mount Sinai Hospital.

Gilbert H. Fletcher, M.D.,* M. D. Anderson Hospital & Tumor Institute, Texas Medical Center, Houston, Texas—American Radium Society and American Club of Therapeutic Radiologists.

Ulrich K. Henschke, M.D.,* Associate Professor of Clinical Radiology, Memorial Hospital for Cancer and Allied Diseases, New York, New York—Memorial Center for Cancer and Allied Diseases.

George C. Lewis, Jr., M.D., Department of Obstetrics and Gynecology, Hahnemann School of Medicine, Philadelphia, Pennsylvania—American College of Obstetrics and Gynecology.

S. Allan Lough, Ph.D., U. S. Atomic Energy Commission, Division of Biology and Medicine, Germantown, Maryland—U. S. Atomic Energy Commission.

Irvin M. Lourie, M.D., Chief, Radiation

and Isotopes Unit, Washington, D. C.—Pan American Health Organization.

Russell H. Morgan, M.D., Radiologist-in-Chief, Johns Hopkins Hospital, Baltimore, Maryland—National Advisory Committee on Radiation.

Robert G. Parker, M.D., Chief, Division of Radiation Therapy, University of Washington, Seattle, Washington—Association of University Radiologists.

Antolin Raventos, M.D.,* Hospital of the University of Pennsylvania, Department of Radiology, Philadelphia, Pennsylvania—Hospital of the University of Pennsylvania.

Milford D. Schulz, M.D.,* Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts—American College of Radiology.

Wendell G. Scott, M.D., Professor of Clinical Radiology, Washington University School of Medicine, St. Louis, Missouri—American Cancer Society.

Michel Ter-Pogossian, Ph.D., Professor of Radiation Physics, Washington University School of Medicine, St. Louis, Missouri—Mallinckrodt Institute of Radiology.

Other persons attending the symposium from the Public Health Service were:

Donald R. Chadwick, M.D., Chief, Division of Radiological Health; DHEW, Public Health Service, Division of Radiological Health, 3rd & Jefferson Drive, S.W., Washington 25, D. C.

Roscoe H. Goeke, M.S., Deputy Chief, State Assistance Branch, Division of Radiological Health; DHEW, Public Health Service, Division of Radiological Health, 3rd & Jefferson Drive, S.W., Washington 25, D. C.

Paul Hahn, Ph.D., Chief, Research Grants Staff, Division of Radiological Health; Woodmont Building, 8120 Woodmont Avenue, Bethesda, Maryland.

* Also served as member of committee drafting conference conclusions.

* Also served as member of committee drafting conference conclusions.

Philip R. Hugill, M.S., Medical Project Officer, State Radioactive Materials Program, State Assistance Branch, Division of Radiological Health; Radiological Health Laboratory, 1901 Chapman Avenue, Rockville, Maryland.

Martha L. Phillips, M.S., Training Grant Officer, Cancer Control Branch, Division of Chronic Diseases; DHEW, Public Health Service, Division of Chronic Diseases, Cancer Control Branch, Washington 25, D. C.

Russell I. Pierce, M.D., Chief, State Assistance Branch, Division of Radiological Health; DHEW, Public Health

Service, Division of Radiological Health, 3rd & Jefferson Drive, S.W., Washington 25, D. C.

John Villforth, M.S., Chief, Assistance to State Radioactive Materials Program, SAB, Division of Radiological Health; Radiological Health Laboratory, 1901 Chapman Avenue, Rockville, Maryland.

The proceedings of this Conference may be obtained from Dr. Donald R. Chadwick, Chief, Division of Radiological Health; DHEW, Public Health Service, Division of Radiological Health, 3rd & Jefferson Drive, S.W., Washington 25, D. C.



NEWS ITEMS

SYMPOSIUM ON RECENT ADVANCES IN NUCLEAR MEDICINE

The Hahnemann Medical College is sponsoring a Symposium on Recent Advances in Nuclear Medicine, to be held at the Marriott Motor Hotel, Philadelphia, Pa., March 19 and 20, 1965.

The Symposium will encompass recent advances in dynamic function studies, instrumentation and organ scanning with radioisotopes.

Inquiries should be directed to Luther W. Brady, M.D., Director, Radiation Therapy, Philadelphia Nuclear Symposium, P.O. Box 46, Jenkintown, Pa., 19046.

SCANNING SYMPOSIUM QUEENS HOSPITAL CENTER

A Scanning Symposium on Occult Bone Metastases for the informal exchange of ideas on radioactive scanning as well as presentation of cases and techniques will be held March 4, 1966, 8:00 P.M., at Queens Hospital Center, with M. David Charkes, M.D., Head, Radioisotope Unit, Albert Einstein Medical Center, Philadelphia, Pa., as the speaker.

Subsequent meetings will be held the first Thursday of each month.

For further information contact Leonard B. Geldman, M.D., Physician-in-charge, Radiation Medicine Department, Queens Hospital Center, 82-68 164th Street, Jamaica 32, N. Y.

POST GRADUATE COURSE IN RADIOTHERAPEUTIC MEDICINE MELBOURNE, AUSTRALIA

The Staff of the Peter MacCallum Clinic and Cancer Institute Board will conduct a Post Graduate Course of instruction in Radiotherapeutic Medicine suitable for candidates preparing for Part II of specialist diplomas in radiotherapy held by the College of Radiologists of Australasia, Uni-

versity bodies and similar organizations. The course will also be suitable for those seeking refresher instruction in radiotherapy.

The course is full time, of 6 weeks' duration and will consist of 60 lectures and 60 lecture demonstrations and practical classes in the Principles and Practice of Radiotherapy, Pathology and Radiobiology.

The course will commence on May 24, 1965 and end on July 2, 1965.

Full particulars and application forms are available on request. Entries for the course will close on April 1, 1965.

All inquiries and correspondence should be addressed to R. K. Churches, The Administrative Secretary, Education Committee, Cancer Institute Board, William Street, Melbourne, Australia.

THE BRITISH INSTITUTE OF RADIOLOGY ANNUAL CONGRESS AND EXHIBITION

The Annual Congress and Exhibition of the British Institute of Radiology will be held April 8 and 9, 1965 at the School of Pharmacy, 29-39 Brunswick Square, London, W.C.1.

The program includes a joint meeting of the Sections on Radiodiagnosis and Radiotherapy, the topic being Carcinoma of the Esophagus; 2 separate meetings of the Section of Radiodiagnosis with the topics of the Early Radiological Management of Head Injuries, and the Early Manifestation of Arthritis; and 2 separate meetings of the Section on Radiotherapy with the topics of Osteogenic Sarcoma and Dosimetry at Interfaces.

The Mackenzie Davidson Memorial Lecture will be delivered by Dr. Hugh Davies on Friday, April 9th, at 5:15 P.M. in the Assembly Hall. His subject will be Three Score Years and Ten.

The Scientific Exhibitions will consist of

instruments, models, diagrams, charts and films illustrating work in the fields of Radiodiagnosis, Radiotherapy, Radiobiology and Physics.

The Annual Dinner of the Institute will take place for members and their guests on Thursday evening, April 8th. This function will be held at the Café Royal, Regent Street, London, W.1, and will be followed by an informal dance.

Attendance at any part of the Congress other than the Memorial Lecture will be restricted to those who have applied for registration as a member of the Annual Congress.

All correspondence concerning the Annual Congress should be addressed to the General Secretary, British Institute of Radiology, 32 Welbeck Street, London, W.1, England. The envelope should be marked "Annual Congress."

FIRST CARIBBEAN CONGRESS OF RADIOLOGY

The First Caribbean Congress of Radiology is being organized by the Department of Radiology at the University of the West Indies in conjunction with the Committee on Post Graduate Studies of the Faculty of Medicine.

The Congress will take place over five days from the 23rd to the 27th of March, 1965. The time, towards the end of the tourist season, has been particularly selected as the climate may be expected to be pleasant and comfortable for all visitors.

An interesting program has been prepared, each morning and afternoon session being devoted to a particular aspect of Radiology. The introductory theme will place emphasis on Geographical Pathology and some comparative aspects of African and Caribbean Pathology will be discussed.

Outside contributions are planned and eminent speakers from Africa, Canada, the United States and the United Kingdom are expected.

For further information please contact the Secretary of the Congress, B. Tomlinson, Department of Radiology, University of the West Indies, Kingston, Jamaica.

APPEAL TO MEMBERS OF THE AMERICAN ROENTGEN RAY SOCIETY

The American Roentgen Ray Society empowered Dr. Wendell G. Scott to assemble a complete set of THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE to be presented to the Sociedad Mexicana de Radiología as an expression of esteem.

The following are the remaining issues that are needed: July, 1928; January and February, 1939; July, 1945; and January, 1949.

If you have any of these issues available, please contact Wendell G. Scott, M.D., 100 N. Euclid, St. Louis 8, Missouri.

W. EDWARD CHAMBERLAIN LECTURE

The 1965 Lecture correlating Radiology and Physiology, in the series honoring Dr. W. Edward Chamberlain, Emeritus Professor of Radiology, will be given by Dr. Elliott C. Lasser, Professor of Radiology, University of Pittsburgh School of Medicine, on March 10, 1965 at 4:00 P.M. in the Auditorium of the Temple University School of Medicine, 3400 North Broad Street, Philadelphia, Pennsylvania. The title of Dr. Lasser's lecture is, "Pharmacodynamics of Radio-Opaque Contrast Materials."



BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

THE PHYSICS OF RADIOLOGY. Second Edition. Revised Second Printing. By Harold Elford Johns, M.A., Ph.D., F.R.S.C., LL.D., Professor and Head of the Department of Medical Biophysics; Professor of Physics, University of Toronto; Head, Physics Division, Ontario Cancer Institute, Toronto, Canada. Cloth. Pp. 767, with many tables and figures. Price, \$23.00. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1964.

The revised Second Printing of the Second Edition remains basically unchanged from its widely accepted predecessor which has become a classic of the radiologic literature. Minor alterations and additions, such as an expanded list of references, serve to bring the text up to date in a constantly advancing field of dynamic progress.

Most of the terminology in the text appears in the unaltered original form despite certain recommendations made by the International Commission on Radiological Units in 1963. In the preface the author explains the reason for the continued use of such terms as, for instance, the *exposure dose* and *absorbed dose*, by stating, "We are using the original notation in order that the distinction between the two quantities continues to be emphasized." Likewise, the usage of the conventional symbols for roentgen (r) and curie (c) is maintained.

The organization of the chapters follows an orderly pattern. The first few chapters deal with basic concepts such as the structure of matter and radiation, the production and properties of x rays and the fundamentals of nuclear physics.

A chapter on discussion, with splendid illustrations, of the radiation apparatus precedes sections on radiation absorption and measurements. A major supplement to these sections is the inclusion in the Appendix of extensive tables on depth dose and absorption coefficients, as well as of other helpful references to scatter functions and roentgen to rad conversions.

Of particular interest to all workers concerned with radiant energy is a chapter on radiation protection.

Specifically included for the benefit of radiotherapists are chapters analyzing the different types of rotation therapy and describing the application of radium, cobalt 60 and cesium 137 in various forms of treatment.

Rounding out the broad scope of this excellent book are chapters dealing with the clinical use of isotopes, radiobiology, and with the physical principles of diagnostic radiology.

The material is presented with great authority in a concise yet remarkably complete manner, appealing both to student and teacher. The many diagrams, graphs and examples of problems to be solved are of immeasurable aid in rendering the subject matter lucid and easy to comprehend. For greater interest to the reader, the problems are dealt with at the end of most chapters, while the answers are listed in the back of the book.

The Physics of Radiology is an extremely valuable source of basic and advanced information for practical use and should form an indispensable part of every radiologic library.

G. MADDOCK, M.D.

ATOMIC MEDICINE. Edited by Charles F. Behrens, M.D., F.A.C.R., Rear Admiral, MC, U. S. Navy (ret.); Roentgenologist, Yater Clinic, Washington, D. C.; Consultant and Lecturer in Radiology, U. S. Naval Medical Center, Bethesda, Md.; Formerly, Director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department; Commanding Officer, Navy Medical Research Institute, National Naval Medical Center, Bethesda, Md.; and E. Richard King, M.D., Captain MC, U. S. Navy (ret.); Professor and Chairman of Division of Radiation Therapy and Nuclear Medicine, Department of Radiology, U. S. Naval Hospital, Bethesda, Md. Fourth edition. Cloth. Pp. 766, with many illustrations. Price, \$18.00. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore 2, Md., 1964.

In its Fourth Edition this standard reference has been considerably revised. Among its best features in the past was a group of chapters by E. P. Cronkite, V. P. Bond and R. A. Conrad

on the nature of radiation injury, its evolution and treatment. These chapters now include sections on the management of radiation injury in nuclear war, and otherwise incorporate new material. The most substantial changes, however, have been made in those chapters which deal with clinical nuclear medicine. New additions include sections on isotope dilution and space studies, iodine diagnosis and treatment of thyroid disease, scintillation scanning, hematologic studies, and a notable section on blood volume by S. N. Albert. A good chapter on therapy with radiocolloids by E. R. King has been preserved, while new material on gastrointestinal and circulatory diagnostic studies and radiotherapeutic applications of radiophosphorus is to be found in the greatly augmented clinical section.

The book is now a more useful instrument than it has been in its previous editions. As a text in clinical nuclear medicine, it is reaching a competitive status with existing ones, while preserving its excellent opening chapters on the radiation syndrome in man.

This book should be available in the library of every teaching Clinical Nuclear Medicine Department.

FREDERICK J. BONTE, M.D.

RADIOLOGIC DIAGNOSTIC AGENTS: a COMPILATION. By William H. Strain, Ph.D., Research Associate, Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.; Stanley M. Rogoff, M.D., Professor of Diagnostic Radiology, Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.; Robert H. Greenlaw, M.D., Associate Professor, Department of Radiology, University of Kentucky College of Medicine, Lexington, Ky.; Renner M. Johnston, M.D., Formerly, Research Assistant, Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.; Felix Huegin, M.D., Formerly, Research Instructor, Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y., and William P. Berliner, B.A., Research Assistant, Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. A Kodak Publication, Volume 40, Supplement, 1964, to *Medical Radiography and Photography*. Paper. Pp. 110, with many

illustrations, Eastman Kodak Company, Rochester, N. Y., 1964.

This is the first professional Manual of Radiologic Diagnostic Agents—chemicals used by physicians to locate defects in the structure and function of various organs.

These agents are divided into two groups: (1) Contrast agents which may be swallowed or injected to absorb roentgen rays and thus produce an outline of the selected organ on a roentgenographic film; and (2) radioactive labeled agents which enable the study of thyroid disease and the location of blood clots, tumors and other abnormalities.

The principal author of the book is Professor William H. Strain of the University of Rochester School of Medicine and Dentistry. He was assisted by Dr. Stanley M. Rogoff, Dr. Renner M. Johnston, Dr. Felix Huegin, and William P. Berliner of the University of Rochester and Dr. Robert H. Greenslaw, now at the University of Kentucky. Dr. Strain and the co-authors worked in cooperation with the editor, William S. Cornwell, of *Medical Radiography and Photography* and many reference assistants.

The publication gives generic names, trade names, chemical names, and composition of all the diagnostic agents developed throughout the world since the discovery of roentgen rays in 1895. It also includes historic outlines of the development of these agents and the biographies of scientists who contributed to this development.

The compilation was distributed at no charge to 50,000 physicians and others who work with radiologic diagnostic agents.

Preparation of the publication was supported in part by grants from the U. S. Public Health Service through the National Institutes of Health and the Division of Radiological Health, Bureau of State Services.

T. LEUCUTIA, M.D.

BOOKS RECEIVED

RESPONSE OF THE NERVOUS SYSTEM TO IONIZING RADIATION. Second International Symposium held at the University of California, Los Angeles. Edited by Thomas J. Haley, Ph.D., Laboratory of Nuclear Medicine and Radiation Biology, University of California, Los Angeles, Calif.; and Ray S. Snider, Ph.D., School of Medicine and Dentistry, University of Rochester, Rochester, N. Y. Cloth. Pp. 768, with 392 illustrations. Price, \$18.50. Little, Brown and Company, Boston, Mass. 02106, 1964.

- CLASSIC DESCRIPTIONS IN DIAGNOSTIC ROENTGENOLOGY. In Two Volumes. Edited by André J. Bruwer, M.B., Ch.B. (University of Cape Town), M.S. (University of Minnesota), Roentgenologist, Tucson Medical Center, Tucson, Ariz.; Research Associate, University of Arizona, Tucson, Ariz.; Formerly, Consultant in Diagnostic Roentgenology, Mayo Clinic, Rochester, Minn. Cloth. Pp. for two volumes, 2059, with many illustrations. Price, \$49.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1964.
- CEREBRAL PALSY. By Sidney Keats, B.S., M.D., Attending Surgeon, New Jersey Orthopedic Hospital; Medical Director, Cerebral Palsy Rehabilitation Institute, Hospital Center, Orange, N. J.; Medical Director, Passaic County Elks Cerebral Palsy Treatment Center, Clifton, N. J.; Former Medical Director, Crippled Children Commission, State of New Jersey. Cloth, Pp. 369, with some tables. Price, \$12.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1965.
- MEDICAL RADIOGRAPHIC TECHNIC. Third edition. Rewritten by William L. Bloom, Jr., John L. Hollenbach, R.T. (ARRT), and James A. Morgan, R.T. (ARRT), Technical Service, X-Ray Department, General Electric Company. Originally under the editorial supervision of Glenn W. Files (1897-1945). Cloth. Pp. 351, with many illustrations. Price, \$11.00. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1964.
- MEDICAL USES OF Ca^{47} : SECOND PANEL REPORT. Report of the Second Panel on the medical uses of Ca^{47} held in Vienna, September 9-11, 1963. International Atomic Energy Agency, Vienna, 1964, Technical Reports Series No. 32. Paper. Pp. 198, with many tables. Price, \$4.00. National Agency for International Publications, Inc., 317 East 34th Street, New York, N. Y. 10016, 1964.
- ULTRASOUND AS A DIAGNOSTIC & SURGICAL TOOL. Based on the International Symposium held at the Royal College of Surgeons, London, December 5, 6, 1962. Edited by Douglas Gordon, M.B., D.M.R., D.M.R.D. Cloth. Pp. 413, with many illustrations. Price, \$10.50. The Williams & Wilkins Company, Baltimore 2, Md., 1964.
- ASCITES TUMORS—YOSHIDA SARCOMA AND ASCITES HEPATOMA(S). National Cancer Institute Monograph No. 16. Sponsored by : Sasaki Institute, Japan; Cancer Institute, The Japanese Foundation for Cancer Research, Japan; National Cancer Institute, U.S.A.; and Ministry of Education, Japan (Monbu-Sho). Edited by Tomizo Yoshida. Cloth. Pp. 289, with many illustrations. Price, \$3.25. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402, 1964.
- THE MALTREATED CHILD; THE MALTREATMENT SYNDROME IN CHILDREN. By Vincent J. Fontana, M.D., F.A.A.P. Director of Pediatrics, St. Vincent's Hospital and Medical Center of New York; Medical Director, New York Foundling Hospital, New York, N. Y. Cloth. Pp. 67, with some illustrations. Price, \$5.00. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1964.
- URETHRAL LESIONS IN INFANCY AND CHILDHOOD: STUDIED BY MICTURITION CYSTO-URETHROGRAPHY. By Edmund H. Burrows, M.B., Ch.B. (Cape Town), M.Rad., D.M.R.D. (Liverpool), Visiting Fellow in Pediatric Radiology, Children's Hospital, Denver, Colo. Cloth. Pp. 112, with many illustrations. Price, \$5.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1964.
- RADIATION BIOCHEMISTRY. Translated from Russian. By A. M. Kuzin. Academy of Sciences of the U.S.S.R., Institute of Biophysics. Cloth. Pp. 284, with some figures. Price, \$13.50. Israel Program for Scientific Translations, Jerusalem, 1964. In U.S.A., Daniel Davey & Co., Inc., 257 Park Avenue South, New York, N. Y., 1964.
- ATLAS DE RADIOLOGIE CLINIQUE DU TUBE DIGESTIF. In Two Volumes. By Marcel Brombart, Chef du Service de Radiodiagnostic à la Clinique César-de-Paepe, Bruxelles, with the collaboration of Henri Monges, Professeur à la Faculté de Médecine de Marseille. Cloth. Pp. for two volumes, 726, with 1227 figures. Price, 350 F. Masson & Cie, Éditeurs, 120, Boulevard Saint-Germain, Paris, France, 1964.
- THE HISTORY OF SURGICAL ANESTHESIA. By Thomas E. Keys, A.B., M.A., Librarian of the Mayo Clinic, Rochester, Minn.; Associate Professor of History of Medicine, Mayo Foundation, Graduate School, University of Minnesota; Honorary Member, American Society of Anesthesiologists. Paper. Pp. 193, with some illustrations. Price, \$2.00. Dover Publications, Inc., 180 Varick Street, New York 14, N. Y., 1964.
- LE ESPERIENZE RADIOGRAFICHE NELLA EVOLUZIONE DELLO STUDIO ANATOMICO DEL SISTEMA LINFATICO DELL'UOMO. By L. Oliva and C. Stuart. Relazione al XXIII Convegno della Società Italiana di Anatomia, Siena, October 14-17, 1963. Paper. Pp. 393, with some illustrations. Valsalva, Editrice, Firenze, Italy, 1964.
- SYMPOSIUM ON MOLECULAR ACTION OF MUTAGENIC AND CARCINOGENIC AGENTS. Sponsored by The Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn. Given at the Research Conference for Biology and Medicine of the Atomic Energy Commission, Gatlinburg, Tenn., April 6-9, 1964. Reprinted from "Journal of Cellular and Comparative Physiology," Volume 64, Supplement 1, October, 1964. Paper. Pp. 191, with some figures. The Wistar Institute of Anatomy and Biology, Philadelphia, Pa., 1964.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

- AMERICAN ROENTGEN RAY SOCIETY**
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Hilton Hotel, Washington, D. C., Sept. 28-Oct. 1, 1965.
- AMERICAN RADIUM SOCIETY**
Secretary, Dr. John L. Pool, 444 East 68th Street, New York, N. Y. 10021. Annual meeting: Roosevelt Hotel, New Orleans, La., April 8-10, 1965.
- RADIOLOGICAL SOCIETY OF NORTH AMERICA**
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Nov. 28-Dec. 3, 1965.
- AMERICAN COLLEGE OF RADIOLOGY**
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting to be announced.
- SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION**
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eight Ave., Spokane 4, Wash. Annual meeting: New York, N. Y., June 20-24, 1965.
- AMERICAN BOARD OF RADIOLOGY**
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1965 examination will be held at the San Francisco Hilton Hotel, San Francisco, Calif., June 13-18, inclusive. This will be the last time that the Special Examination in Nuclear Medicine will be offered to physicians who are already certified in Radiology or Therapeutic Radiology. The deadline for filing applications for this examination was December 31, 1964. The Fall 1965 examination will be held at the Statler Hilton Hotel, Dallas, Texas, December 5-10, inclusive. The deadline for filing applications for this examination is June 30, 1965.
- AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE**
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.
- AMERICAN CLUB OF THERAPEUTIC RADIOLOGISTS**
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo.
- ELEVENTH INTERNATIONAL CONGRESS OF RADIOLOGY**
Secretary-General, Professor Dr. Med. Arduino Ratti, via Moscová, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy. Meeting: September 22-28, 1965.
- NINTH INTER-AMERICAN CONGRESS OF RADIOLOGY**
Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania. Meeting: Montevideo, Uruguay, 1967.
- ALABAMA RADIOLOGICAL SOCIETY**
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.
- AMERICAN NUCLEAR SOCIETY**
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.
- ARIZONA RADIOLOGICAL SOCIETY**
Secretary-Treasurer, Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.
- ARKANSAS RADIOLOGICAL SOCIETY**
Secretary Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

- ASSOCIATION OF UNIVERSITY RADIOLOGISTS**
Secretary-Treasurer, Dr. Alexander R. Margulis, Department of Radiology, University of California, San Francisco, Calif. Annual meeting: Seattle, Washington, May 14 and 15, 1965.
- ATLANTA RADIOLOGICAL SOCIETY**
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.
- BAVARIAN-AMERICAN RADIOLOGIC SOCIETY**
Secretary, Dr. Roy R. Deffebach, Major, MC, Radiology Service, 5th General Hospital, APO 154, New York, N. Y. Meets quarterly.
- BLOCKLEY RADIOLOGICAL SOCIETY**
Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.
- BLUEGRASS RADIOLOGICAL SOCIETY**
Secretary-Treasurer, Dr. Daniel J. Hanson, University of Kentucky, Medical Center, Lexington, Kentucky. Meets quarterly.
- BROOKLYN RADIOLOGICAL SOCIETY**
Secretary, Dr. Jay P. Sackler, Brooklyn, N. Y. Meets first Thursday of each month, October through June.
- BUFFALO RADIOLOGICAL SOCIETY**
Secretary, Dr. Berkeley Zinn, 85 Wehrle Dr., Buffalo 25, N. Y. Meets second Monday evening each month, October to May inclusive.
- CALIFORNIA RADIOLOGICAL SOCIETY**
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.
- CATAWBA VALLEY RADIOLOGICAL SOCIETY**
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Tuesday, Dept. of Radiology, Valde General Hosp., Valde, N. C. at 12:00 P.M.
- CENTRAL NEW YORK RADIOLOGICAL SOCIETY**
Secretary-Treasurer, Dr. Edward W. Carsky, Crouse-Ingving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month, October through May.
- CENTRAL OHIO RADIOLOGICAL SOCIETY**
Secretary-Treasurer, Dr. Harold W. Long, 81 S. Fifth St., Columbus 15, Ohio. Meets third Thursday in October, and second Thursday in November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.
- CENTRAL SOCIETY OF NUCLEAR MEDICINE**
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.
- CHICAGO ROENTGEN SOCIETY**
Secretary-Treasurer, Dr. Robert D. Moseley, Jr., Dept. of Radiology, Univ. of Chicago, 950 E. 59th St., Chicago 37, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at 8:00 P.M.
- CLEVELAND RADIOLOGICAL SOCIETY**
Secretary-Treasurer, Dr. James Christie, 10515 Carnegie Avenue, Cleveland, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.
- COLORADO RADIOLOGICAL SOCIETY**
Secretary, Dr. David J. Stephenson, 8300 West 38th Ave., Wheat Ridge, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.
- CONNECTICUT VALLEY RADIOLOGIC SOCIETY**
Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

* Secretaries of societies are requested to send timely information promptly to the Editor.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary, Dr. R. E. Collier, 3500 Gaston Ave., Dallas, Tex. Meets monthly, third Monday, at Southwest International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY

Secretary, Dr. Arch H. Hall, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY

Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. C. H. Kimball, 2200 Harris Circle, Cleveland, Tenn. Meets in January and September.

EASTERN RADIOLOGICAL SOCIETY

Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. Andre S. Capri, 3471 N. Federal Highway, Fort Lauderdale, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

GEORGIA RADIOLOGICAL SOCIETY

Secretary, Dr. David Robinson, P.O. Box 394, Savannah, Ga. Meets in spring and fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Oliver P. Winslow, Jr., Baptist Hospital of Miami, Inc., 8900 S. W. 88th St., Miami 56, Fla. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS

Secretary, Dr. C. M. Witt, #16 Hampton Village Plaza, St. Louis 9, Mo.

HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. D. A. Van Velzer, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

IDAHO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY

Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC.

Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY

Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. R. F. Conrad, Newman Memorial Hospital, Emporia, Kan. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER, AMERICAN COLLEGE OF RADIOLOGY

Secretary-Treasurer, Dr. Robert H. Greenlaw, Dept. of Radiology, Univ. of Kentucky Med. Ctr., Lexington, Ky. Meetings will be semiannually.

KENTUCKY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Stanley Dannenberg, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY

Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LOS ANGELES RADIOLOGICAL SOCIETY

Secretary, Dr. Austin R. Wilson, 540 N. Central Ave., Glendale, Calif. 91203. Meets second Wednesday of month in November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Annual midwinter meeting to be announced.

MAINE RADIOLOGICAL SOCIETY

Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Waterville, Me. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY

Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Maryland.

MEMPHIS ROENTGEN SOCIETY

Secretary-Treasurer, Dr. Irving K. Ettman, 684 W. Brookhaven Circle, Memphis, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Alexander W. Friedman, Mid-Hudson Medical Group, Fishkill, N. Y. Meets 7:00 P.M., first Wednesday of each month September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary-Treasurer, Dr. Harold F. Ibach, 2400 W. Villard Avenue, Milwaukee 9, Wis. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Frank J. Anderson, 810 E. 27th St., Minneapolis 7, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MISSOURI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

MONTANA RADIOLOGICAL SOCIETY

Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY

Secretary, Dr. Perry R. Mandel, Nassau Hospital, Mineola, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY

Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

NEW ENGLAND ROENTGEN RAY SOCIETY

Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month, October through April, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY

Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW MEXICO ASSOCIATION OF RADIOLOGISTS

Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

NEW MEXICO SOCIETY OF RADIOLOGISTS

Secretary, Dr. William G. McPherson, Hobbs, New Mexico. Four annual meetings, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW MEXICO ROENTGEN SOCIETY

Secretary, Dr. Harry Z. Mellins. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M., Annual Spring Conference: Waldorf-Astoria Hotel, April 29, 30 and May 1, 1965.

NORTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

NORTH DAKOTA RADIOLOGICAL SOCIETY

Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY

Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY

Secretary, Dr. John M. Johannessen, Mercy Hospital, Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

OHIO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. M. M. Thompson, Jr., 316 Michigan St., Toledo 2, Ohio. Annual meeting: Terrace Hilton Hotel, Cincinnati, Ohio, May, 1965.

OKLAHOMA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Dave B. Lhevine, B10 Doctors Bldg., 2021 South Lewis, Tulsa, Okla. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Herbert H. Benson, 100 East Valencia-Mesa Dr., Fullerton, Calif. Meets fourth Tuesday of every month in Orange County Medical Association Building.

OREGON RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. James A. Schneider, St. Vincent Hospital, Portland 10, Ore. Meets on second Wednesday of month at 7:00 P.M. at the University Club, Portland, Ore.

ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY

Secretary, Dr. Willis Taylor, Seattle, Washington. Annual meeting to be announced.

PENNSYLVANIA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Pittsburgh Hilton Hotel, May 21-22, 1965.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. Antolin Raventos, Hospital of the University of Pennsylvania, Philadelphia 4, Pa. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY

Secretary, Dr. Robert N. Berk, 3305 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SOCIETY OF CONNECTICUT

Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450 Chapel St., New Haven 11, Conn. Meetings are held bimonthly.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI

Secretary, Dr. Harold N. Margolin, 6159 Tulane Road, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY

Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF HAWAII

Secretary, Dr. Russell E. Graf, P.O. Box 294, USA Tripler General Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA

Secretary, Dr. Andrew F. Giesen, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

RADIOLOGICAL SOCIETY OF NEW JERSEY

Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK

Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA

Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA

Secretary-Treasurer, Dr. John L. Gwinn, Children's Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles, Calif. 90027. Meets three times a year, usually October, February, and May.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY

Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.

Secretary, Dr. Irving B. Joffe, Rochester General Hospital, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting to be announced.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY

Secretary, Dr. Hugh F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Charles P. Hyslop, 7901 Frost St., San Diego 22, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY

Secretary, Dr. Malcolm Jones, University of California Hospital, San Francisco 22, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION

Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA

Secretary-Treasurer, Dr. Martin A. Thomas, 1150 Connecticut Ave., Washington 36, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION

Secretary, Dr. Andrew F. Giesen, Jr., Drawer M-M, White-Wilson Clinic, Fort Walton Beach, Florida 32548. Annual meeting: Houston, Texas, Nov. 1-4, 1965.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION

Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, Los Angeles 27, Calif. Annual meeting: Hilton Hotel, Washington, D. C., Sept. 27, 1965.

SOCIETY OF NUCLEAR MEDICINE

Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Bal Harbour, Fla., June 17-19, 1965.

SOUTH BAY RADIOLOGICAL SOCIETY

Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Paul L. Clemetson, 877 W. Fremont Ave., Suite C-3, Sunnyvale, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTH DAKOTA RADIOLOGICAL SOCIETY

Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

SOUTHERN RADIOLOGICAL CONFERENCE

Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting to be announced.

SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY

Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Tex. Annual meeting to be announced.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY

Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Carlisle C. Smith, Salt Lake General Hospital, 2033 S. State St., Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY

Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

WASHINGTON STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. Karl J. Myers, The Myers Clinic-Broadus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER RADIOLOGICAL SOCIETY

Secretary, Dr. Joel J. Schwartzman, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY

Secretary, Dr. Charles Benkendorf, 408 St. Francis St., Green Bay, Wis. Meets twice a year, May and September.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIOLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.

Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR

Secretary, Dr. Rafael Vaga Gómez.

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA

Secretary, Dr. Carlos E. Escobar, 9^a. Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA CUBANA

Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA

Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A.C.

Calle del Oro No. 15, México 7, D. F.

Secretary-General, Dr. E. Alvarez Hernández.

Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLOGICA PANAMEÑA

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

SOCIEDAD RADIOLOGICA DE PUERTO RICO

Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC

Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

CANADIAN ASSOCIATION OF PHYSICISTS, DIVISION OF MEDICAL AND BIOLOGICAL PHYSICS.

Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY

Secretary, Dr. J. T. Mason, 540 Tegler Bldg., Edmonton, Alberta, Canada. Meets second Tuesday of each month, October to May.

FACULTY OF RADIOLOGISTS

Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: Cambridge, England, June 18-19, 1965.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS IN IRELAND

Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)

Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

CANADIAN ASSOCIATION OF RADIOLOGISTS

Honorary Secretary-Treasurer, Dr. D. J. Sieniewicz, *Associate Honorary Secretary-Treasurer*, Dr. Maurice Dufresne, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting to be announced.

MONTREAL RADIOLOGICAL STUDY CLUB

Secretary, Dr. Leonard Rosenthal, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION

Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTRO-RADIOLOGIE MÉDICALE

General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Que., Canada. Meets third Saturday each month.

TORONTO RADIOLOGICAL SOCIETY

Secretary, Dr. Wallace M. Roy, St. Joseph's Hospitals, 30 The Queensway, Toronto 3, Ont., Canada. Meets second Monday of each month, September through May.

COLLEGE OF RADIOLOGISTS OF AUSTRALASIA

Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

SOUTH AMERICA

ASOCIACIÓN ARGENTINA DE RADIOLOGÍA

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

ATENEO DE RADIOLOGIA

Secretary, Dr. Victor A. Añños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

COLÉGIO BRASILEIRO DE RADIOLOGIA

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

SOCIEDAD ARGENTINA DE RADIOLOGIA

Secretary, Dr. Armando B. de Onaindia, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

SOCIEDAD BOLIVIANA DE RADIOLOGÍA

Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

SOCIEDADE BRASILEIRA DE RADIOLOGIA

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

SOCIEDAD CHILENA DE RADIOLOGÍA

Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

SOCIEDAD COLOMBIANA DE RADIOLOGIA

Secretary, Dr. Armando Uribe, Hospital Militar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

SOCIEDAD ECUATORIANA DE RADIOLOGÍA Y FISIOTERAPIA

Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador.

SOCIEDAD PARAGUAYA DE RADIOLOGÍA

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

SOCIEDAD PERUANA DE RADIOLOGIA

Secretary, Dr. Vicente Ubillus, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

SOCIEDAD DE RADIOLOGICA DEL ATLANTICO

Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FÍSICA MÉDICA DEL URUGUAY

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

SOCIEDADE DE RADIOLOGIA DE PERNAMBUCO

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

SOCIEDAD DE ROENTGENOLOGIA Y MEDICINA NUCLEAR DE LA PROVINCIA DE CÓRDOBA

Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

SOCIEDAD VENEZOLANA DE RADIOLOGÍA

Secretary-General, Dr. Rubén Merensfeld, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

CONTINENTAL EUROPE

ÖSTERREICHISCHE RÖNTGEN-GESELLSCHAFT

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

SOCIÉTÉ BELGE DE RADIOLOGIE

General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

SOCIÉTÉ EUROPÉENNE DE RADIOLOGIE PÉDIATRIQUE

Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France. *General Secretary*, Dr. Ole Eklöf, P.O. Box, Stockholm 60, Sweden. Annual meeting: Stockholm, Sweden, May 20-22, 1965.

SOCIÉTÉ FRANÇAISE D'ELECTRORADIOLOGIE MÉDICALE, and its branches: SOCIÉTÉ DU SUD-OUEST, DU LITTORAL MÉDITERRANÉEN, DU CENTRE ET DU LYONNAIS, DU NORD, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8e, France.

ČESKOSLOVENSKÁ SPOLEČNOST PRO ROENTGENOLOGII A RADIOLOGII

Secretary, Dr. Robert Poch, Praha 12, Srobarova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

DEUTSCHE RÖNTGENGESELLSCHAFT

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.

SOCIETÀ ITALIANA DI RADIOLOGIA MEDICA E DI MEDICINA NUCLEARE

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

NEDERLANDSE VERENIGING VOOR RADIOLOGIE

Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

SCANDINAVIAN ROENTGEN SOCIETIES

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

SOCIEDAD ESPAÑOLA DE RADIOLOGÍA Y ELECTROLOGÍA MÉDICAS Y MEDICINA NUCLEAR

Secretary, Dr. D. Aureo Gutierrez Churruga, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

SCHWEIZERISCHE GESELLSCHAFT FÜR RADIOLOGIE UND NUKLEARMEDIZIN (SOCIÉTÉ SUISSE DE RADIOLOGIE ET DE MÉDECINE NUCLÉAIRE)

Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

ASIA

INDIAN RADIOLOGICAL ASSOCIATION

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

INDONESIAN RADIOLOGICAL SOCIETY

Secretary, Professor Sjahriar Rasad Taman Tjut Mutiah 1, Diakarta, Indonesia.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

PAILLAS, J.-A., BONNAL, J., PAYAN, H., and PRUVOST, A. Les thromboses puerpérales du sinus longitudinal supérieur: (deux observations). (Puerperal thromboses of the superior longitudinal sinus; report of 2 cases.) *Presse méd.*, Sept., 1964, 72, 2265-2268. (From: Clinique neuro-chirurgicale de l'Hôpital de la Timone, Faculté de Médecine de Marseille, France.)

The occurrence of cerebral thrombophlebitis in the puerperal state has been recognized for a long time. In 1828, Menière, and a year later, Tomell, reported their observations on such cases. In 1937, Symonds and Martin presented the hypothesis of retrograde propagation of thrombophlebitis of the pelvic veins to the cerebral veins via the vertebral venous plexuses. This occurs under the influence, or as a result, of abdominal compression and increased effort, and is confirmed by the works of Garcin Pestel, reported in 1949, as well as by several other reports which have since appeared.

Complete thrombosis of the superior longitudinal sinus is very serious and rapidly leads to death. Of less frequent occurrence is partial thrombosis, which the patient often survives, with residual complications.

The authors report 2 cases of superior longitudinal sinus thrombosis occurring in the puerperal period, 1 ending in death and 1 surviving but retaining permanent complications—hemiplegia and epilepsy.

The first patient developed symptoms following premature delivery with subsequent phlebitis of the left lower extremity for which anticoagulant therapy was administered. She developed repeated Jacksonian seizures, coma and, eventually, died. Cerebral angiography revealed slow circulation, absence of opacification of the superior sagittal sinus and of the cortical veins, and increased opacification of the inferior longitudinal sinus and of the sylvian veins. At autopsy, complete thrombosis of the superior sagittal sinus was present, with cerebral softening and considerable cerebral hemorrhage.

The second patient presented a history of repeated attacks of thrombophlebitis of the lower extremity, following several pregnancies, some of which ended in abortion. Following the last pregnancy, partial thrombosis of the superior longitudinal sinus developed. The patient remained an invalid and retained permanent damage, with hemiplegia and repeated Jacksonian seizures.

In fatal cases, superior longitudinal sinus thrombosis is followed by cerebral edema, bilateral hemorrhagic infarction and eventually death. In the non-fatal cases, with regression of symptoms consequent to partial superior sinus thrombosis, the regression of

symptoms and improvement of the clinical condition depend upon the development of supplementary venous circulation through the inferior longitudinal sinus and through the sylvian veins. In this manner, the initial hemorrhagic edema may be drained and permitted to subside.

The authors stress the importance of bilateral carotid angiography from which basic information is obtained on which the diagnosis is made; *i.e.*, slowing of the circulation, absence of opacification of the superior longitudinal sinus as well as of the superior cortical veins, and eventually the development of abnormal venous channels.

Opacification of the superior sagittal sinus by direct injection is considered dangerous and is not recommended by the authors. Neither do they advocate the use of anticoagulants in the treatment of superior longitudinal sinus thrombosis. If anticoagulants are to be helpful, they should be administered early, prior to the development of complete thrombosis.

Reproductions of a set of 4 films from serial angiography and 4 photographs of autopsy specimens from the first case accompany this article.—*William H. Shehadi, M.D.*

BRICE, J. G., and CROMPTON, M. R. Spontaneous dissecting aneurysms of the cervical internal carotid artery. *Brit. M. J.*, Sept. 26, 1964, 2, 790-792. (From: Department of Neurosurgery of St George's Hospital at Atkinson Morley's Hospital, London, England.)

The cause of obstruction of the internal carotid artery in patients below the age of 40 may be obscure. Many are secondary to recent trauma. Other causes mentioned are cerebral aneurysm and subarachnoid hemorrhage, hypertension, blood dyscrasia, chronic infection, neoplasms and the postpartum state. Atheromatous occlusion is rare.

In a series of 115 patients with occlusion of the internal carotid artery in the neck, 3 cases were the result of spontaneous dissecting aneurysm. All 3 patients presented with sudden hemiparesis or hemiplegia following 12 to 48 hours of headache. One patient had blurring of vision in one eye, a characteristic symptom of internal carotid occlusion. Roentgenologically, a tapering type of filling defect on angiography was shown, not unlike that seen in atheromatous lesions. At necropsy there was typical cystic degeneration of the media of the internal carotid and other arteries. All dissections were remote to the site of needle puncture and were thus considered spontaneous. All patients succumbed to massive ipsilateral cerebral infarction.

Of dissections occurring in the carotid and vertebral arterial tree, the majority are located peripherally within the cranial cavity, the middle cerebral artery being most commonly affected. Involvement

of the vessels in the neck is rare. Only 1 case has been reported previously.

The diagnosis should be considered in young patients with sudden hemiplegia and angiographic evidence of the localized irregular tapering defect, so that immediate thromboendarterectomy might change the course of this disease.—*David Corbett, M.D.*

HOWLAND, W. J., and CURRY, J. L. Transient cerebral blindness—a hazard of vertebral artery catheterization: report of four cases. *Radiology*, Sept., 1964, 83, 428-432. (From: Ohio Valley General Hospital, Wheeling, W. Va.)

This is a report of 4 cases of blindness which complicated selective catheter arteriography of brachiocephalic vessels through the aortic arch. In each instance the left vertebral artery was entered inadvertently with a relatively large catheter (Kifa yellow) during attempts to catheterize the left common carotid artery. Fortunately, the blindness was temporary in all 4. In the first 3 cases, its onset took place after the injection of opaque medium; in the fourth, definite visual loss occurred before the selective injection of contrast material.

Because of these occurrences the authors investigated the concept of catheter occlusion of the vertebral artery with consequent hypovascularity of the occipital cortex. An analysis of 34 catheter arch aortograms revealed that the average diameter of each vertebral artery is 0.3 cm. Since the external diameter of the yellow Kifa catheter used in these studies is 0.3 cm. it seems quite obvious that this catheter will completely or almost completely occlude the vertebral artery in many patients. This analysis also revealed that there is no safe level above the aortic arch to which the catheter could be advanced before a test dose was given as the distance from the aortic arch to the origin of the right vertebral artery varied from 2.2 cm. to 7.0 cm. (average 4.2 cm.), while on the left the variation was from 1.7 cm. to 6.7 cm. (average 3.9 cm.).

The authors feel that the premise that free aspiration of blood after catheter placement is evidence that there is no catheter obstruction of the artery is not valid. They feel that with "tight" catheterization of the vertebral artery the so-called "subclavian steal syndrome" comes into effect. This is in actuality a "catheter vertebral steal" and is due to a reversal of blood flow through the catheterized artery when aspiration through the catheter is done.

The authors conclude that in considering the etiology of transient cerebral blindness the possible direct effects of contrast medium cannot be denied, but these 4 reported cases and those found in the literature suggest a strong relationship to mechanical catheter obstruction of a vertebral artery. They state that careful study of the preliminary arch aortogram

is probably the best method to avoid inadvertent catheterization of the vertebral artery.—*Donald N. Dysart, M.D.*

DILENCE, D., FISCHGOLD, H., and DAVID, M. Sémiologie de l'ophtalmique après soustraction: aspects normaux et pathologiques. (Ophthalmic diagnosis with subtraction: normal and pathologic aspects.) *An. med.*, Barcelona, 1963, No. 4, 145-157. (Address: Prof. H. Fischgold, Service de Neuro-radiologie de l'Hôpital de La Pitié, Paris, France.)

With the usual arteriographic techniques it is difficult to see vessels in the orbit less than 0.8 mm. in diameter. By means of subtraction, vessels down to less than 0.5 mm. in diameter may be visualized.

With the aid of subtraction technique deformity of vessels produced by tumors, tumor vessels, vascular malformations, and the collateral flow from the external carotid artery may be demonstrated.—*Charles M. Nice, Jr., M.D., Ph.D.*

NECK AND CHEST

STOKER, D. J. Histoplasmosis in Cyprus: report of two cases. *Brit. M. J.*, Sept. 26, 1964, 2, 793-795. (From: Metabolic Unit, St. Mary's Hospital, Paddington, London, England.)

More than half the cases of histoplasmosis reported outside North America have been in Central and South America. Other principal endemic areas include Africa and the Far East (Phillipines, Indonesia and Australia). The disease is rather rare in Great Britain with only 6 case reports from 1906 to 1955, compared to an estimated 25 to 30 million people in the United States who have experienced some form of *Histoplasma* infection. Studies in England, Greece, Turkey and Cyprus show approximately 2 per cent positive reactors to the histoplasmin skin test. No previous case of histoplasmosis occurring in Cyprus has been published.

The present report deals with 2 British subjects, resident in Cyprus, who developed acute diffuse pulmonary histoplasmosis, with rather characteristic miliary parenchymal lesions demonstrated roentgenographically. In 1 patient there was a complicating encephalitis. Both patients were members of a party visiting a labyrinth in the ancient Roman Settlement of Curium. While in the cave, each patient handled a bat. Evidently the bat excreta together with the warm moist atmosphere of the cave provided ideal conditions for saprophytic mycelial growth of the fungus.—*David Corbett, M.D.*

SCHOBER, R. Selektive Bronchialisarteriographie. (Selective bronchial arteriography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1964, 101, 337-348.

(Address: Oberarzt des Universitätsstrahleninstitutes, 665 Homburg/Saar, Germany.)

The blood supply in the lungs is composed of the pulmonary arteries or functional system, the bronchial arteries or nutritive element, and numerous precapillary broncho-pulmonary anastomoses. Virchow showed that closure of a pulmonary branch was followed by dilatation and an increase in number of bronchial arteries in the affected area. Variations of this process occur in congenital heart disease, such as pulmonary stenosis or atresia and in transposition of the great vessels, but also in acquired mitral stenosis.

By means of selective bronchial arteriography, much more detailed information can be gained about many diseases that involve the lungs. In tuberculosis, the bronchial arteries form a network around the caseous focus and the corresponding pulmonary arteries become thrombosed. Recanalization of the latter takes place via broncho-pulmonary anastomoses. The bronchial arteries are responsible for the liquefaction of the caseous material. In bronchiectasis, chronic pneumonia or lung abscess, the peribronchial arteries become thicker and more abundant, partly because of an increase in precapillary anastomoses with branches of the pulmonary arteries. In pulmonary emphysema, the vessels are decreased in width and number. In carcinoma, the bronchial circulation forms a thick network in which individual vessels are irregularly arranged and show considerable variation in caliber; the pulmonary arteries assume a more passive role and become partially occluded.

The technique consists of inserting a catheter (Type Kifa red) through the femoral artery and advancing it in contact with the anterior wall of the aorta until the desired level is reached. This is a matter of experience but when the bronchial artery is entered, a mild cough reflex is produced in most patients, especially if a check is made at that time with an injection of 2-3 cc. of the contrast material. Should an intercostal artery be entered, the patients generally experience a feeling of warmth in the back. An injection of 5 cc. of urografin 60 per cent is adequate for this investigation. The only contraindication to the method is a specific sensitivity of the patient to the contrast medium.—*J. Zausner, M.D.*

TOURNIAIRE, A., BLUM, J., TARTULIER, M., and DEYRIEUX, F. Coeur pulmonaire chronique sclérodermique. (Sclerodermic chronic cor pulmonale.) *Presse méd.*, Sept., 1964, 72, 2269-2272. (From: Service de Cardiologie et Laboratoire d'Exploration fonctionnelle cardiopulmonaire, Hôpital Saint-Joseph, Lyon, France.)

Pulmonary complications of scleroderma have been described late in the last century. The incidence has been variously reported by different authors. In a series of 31 cases (Piper and Helwig, 1955) pulmo-

nary fibrosis occurred in 25. More recently (1961), Tuffanelli and Winkelman found an incidence of 24 per cent in a series of 550 patients with scleroderma. Rubin (1956) believes that pulmonary scleroderma may occur without cutaneous scleroderma. Unfortunately, the diagnosis of primary pulmonary scleroderma cannot be readily confirmed because of the absence of characteristic histologic findings or diagnostic criteria.

Pulmonary function studies demonstrate an alteration or decrease of pulmonary ventilation, and a limited or decreased capacity of the alveolar-capillary diffusion. Other workers report pulmonary arterial hypertension as a significant finding.

Frequently, a roentgenologic examination of the chest reveals a diffuse reticular-nodular type of infiltration, more prominent in the lower lung fields. However, often pulmonary sclerodermic fibrosis may be present without being roentgenologically demonstrable and is severe enough to interfere with alveolar-capillary diffusion and pulmonary circulation. Consequently, the diagnosis will be made on the basis of pulmonary function studies, a study of hemodynamics and a pulmonary biopsy.

The authors present a case of chronic sclerodermic cor pulmonale in which respiratory functional and hemodynamic studies were made with biopsy confirmation. They stress the fact, illustrated in this rare case which they report, of the necessity of performing multiple examinations before a diagnosis can be established. However, they also stress the fact that the most important single test is the determination of the diffusion capacity. Thus, a disturbance of pulmonary diffusion may precede hypoxemia. This test then permits diagnosis of early sclerodermic pulmonary involvement and should be part of a routine examination in all cases of cutaneous scleroderma.—*William H. Shehadi, M.D.*

LILLICRAP, DAVID, and PIESOWICZ, ALINA. Mitral stenosis and systemic emboli. *Brit. M. J.*, Nov. 7, 1964, 2, 1169-1171. (Address: Mr. Lillicrap, Senior Registrar, Guy's Hospital, London, England.)

A 3 year follow-up was done on 84 mitral valvotomy patients over the age of 40. The immediate mortality rate was 6 per cent with an additional 5 per cent occurring during each succeeding year. Of those patients who had not experienced preoperative embolic phenomena, 48 per cent had good results (determined by improvement of exercise tolerance); of those who had preoperative emboli, only 27 per cent achieved good results.

Thirty-four patients had significant mitral incompetence which led to unsatisfactory results or death. Six patients had further emboli at operation and 4 more had emboli during the follow-up period.

The occurrence or threat of emboli is not sufficient reason to perform mitral valvotomy; long-term anti-

coagulant therapy is suggested.—*Lois Cowan Collins, M.D.*

ABDOMEN

VOLLMER, K. Carcinoma of the duodeno-jejunal flexure. *German Med. Monthly*, Oct., 1964, 9, 401-402. (Address: Strahlenabteilung des Krankenhauses "Maria Hilf," Mönchengladbach, Germany.)

Although tumors of the small bowel are the least common of all tumors of the gastrointestinal tract, they are generally found in the region of the ileum. Carcinoma of the duodenum is distinctly rare; and the incidence decreases progressively with increasing distance from the pylorus. There have been numerous reports of carcinoma of the stomach, pancreas and other surrounding structures invading the duodenum and upper jejunum, but even large radiologic reference texts fail to mention primary carcinoma of the duodeno-jejunal flexure.

The author presents a case of carcinoma of the duodeno-jejunal flexure which was diagnosed preoperatively on an upper gastrointestinal examination and completely excised at the time of surgery. Most of the previously reported cases were already inoperable when found, usually at laparotomy for intestinal obstruction.

The author states that by examining the patient in the oblique and head down position with the use of compression to displace the stomach, this area can be adequately visualized fluoroscopically during a barium meal study. If adequate visualization still cannot be obtained, then the examination may be performed by projecting through the stomach after first filling it with air. When a lesion is suspected, several spot roentgenograms should be taken because delicate changes in the bowel wall may easily be overlooked at fluoroscopy.—*Kenneth M. Nowicki, M.D.*

REYELT, WALTER, P., JR., and ANDERSON, ARTHUR A. Retrograde jejuno gastric intussusception. *Surg. Gynec. & Obst.*, Dec., 1964, 119, 1305-1311. (From: Department of Surgery, Newington Veterans Administration Hospital, Newington, Conn., and Hartford Hospital, Hartford, Conn.)

Retrograde jejuno gastric intussusception is a rare complication of gastroenterostomy or gastric resection. Either the afferent or efferent jejunal loops, or both, may intussuscept into the stomach.

In the acute form the onset is usually marked by severe, sudden epigastric pain and hematemesis. Physical examination reveals epigastric tenderness and sometimes visible peristalsis. Roentgenographically, gastric dilatation without dilatation of the small intestine is suggestive of this disorder. Immediate contrast studies should be done to make an early

preoperative diagnosis. In a patient with a previous gastrojejunostomy, a partially movable circumscribed filling defect in the stomach with curved lines simulating intestinal folds indicates retrograde intussusception. Other roentgen signs are dilatation of the gastric remnant, delay in emptying, flattening of the greater curvature, edema, and displacement of the antrum toward the right. Emergency surgical intervention is imperative in the acute cases.

In the chronic state, the intussuscepted mass is usually smaller and often is self-reducing, particularly when the patient is erect. Many patients with chronic intussusception do not require surgical intervention, but it is indicated when a patient is severely disabled or malnourished as a result of frequent attacks.—*Lois Cowan Collins, M.D.*

PORTMANN, J. Angiographische Größenbestimmung der Sigma- und Rektum-Karzinome. (Angiographic determination of the extent of carcinomas of the sigmoid and rectum.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1964, 101, 246-252. (Address: Röntgenabteilung Knappschaftskrankenhaus, 425 Bottrop/Westfalen, Germany.)

A knowledge of the vascular anatomy of this region is essential. The sigmoid is supplied by branches of the inferior mesenteric artery (the sigmoid arteries and the superior rectal artery), which arises from the aorta at the level of L3-L4. The rectal ampulla is supplied by the inferior rectal artery and branches of the internal iliac (the pudendal and both the superior and inferior vesical arteries) with some anastomoses from the superior rectal artery.

The technique consists of bilateral femoral injection with urografin 60 per cent manually with a steady and quick motion, using 20 cc. of the contrast medium which is introduced via a Seldinger catheter (PE 205) reaching above the bifurcation of the aorta or approximately a distance of 25-27 cm. A small amount of air is instilled sufficient to distend the distal portion of the colon. Roentgenograms are taken with an automatic cassette changer every second for 10 seconds; one series is taken in the anteroposterior projection; another series is obtained in a 30° obliquity for "bi-planar" visualization. The only preparation necessary is a mild sedative and local anesthesia.

The exact extent of the neoplastic involvement was fully corroborated by surgery in 3 of 5 cases. In the other 2 patients, angiographic studies indicated the inoperability of the invasive tumors. As in other areas, neoplasms are identified by the tumor "staining," so that observation of the venous phase is important. The extent is more easily determined in lesions of the sigmoid than those of the recto-sigmoid.—*J. Zausner, M.D.*

HOLLAND, JAMES M., HASLAM, ROBERT A. H., and KING, LOWELL R. Meconium in the processus vaginalis of infants. *J. Urol.*, Aug., 1964, 92, 140-143. (From: Brady Urological Institute and Harriet Lane Home for Invalid Children of the Johns Hopkins Hospital, and Urology and Pediatric Services of Baltimore City Hospitals, Baltimore, Md.)

Radiologists are familiar with the punctate calcifications which occur within the peritoneal cavity associated with meconium ileum.

In this article the authors report 5 cases of this entity in which the meconium found its way into the scrotum through the processus vaginalis. On roentgenologic examination of these infants, there were stippled calcifications in the abdomen and in the scrotum.

Marked swelling of the scrotum is due to the sterile inflammatory reaction produced by the irritating effect of the meconium with subsequent calcification and fibrosis. The calcification is quite different from that which is seen in some testicular tumors or from other causes.

The authors include 6 illustrations which show the roentgen, gross pathologic, and histologic findings.—*George W. Chamberlin, M.D.*

BROWN, KENNETH A., STAUBITZ, WILLIAM J., OBERKIRCHER, OSCAR J., and NIESEN, WILLIAM C. A review of retroperitoneal fibrosis. *J. Urol.*, Oct., 1964, 92, 323-330. (From: Department of Surgery, Division of Urology, Buffalo General Hospital; Edward J. Meyer Memorial Hospital; and Department of Surgery, Division of Urology, State University of New York at Buffalo, Buffalo, N. Y.)

The authors report 4 additional cases of retroperitoneal fibrosis and review from the literature 71 cases with the express purpose of offering a surgical approach, which has proven valuable for bilateral disease, and to possibly expose a common etiologic factor.

Retroperitoneal fibrosis is a disease of unknown etiology. It is frequently bilateral and somewhat more common in men than in women. The gross pathology of the tissues surrounding the ureters appears as a grayish-white fibrous plaque which may extend from the renal hilus to the bladder and may be from a few millimeters to several centimeters in thickness. It is adherent to the posterior peritoneum but usually does not invade the muscle and can be easily stripped at a cleavage point. Microscopically, the involved tissue is found to be composed of collagen fibers, inflammatory cells, fibroblasts, fat cells, eosinophils, and mononuclear cells with occasional foreign body giant cells.

Clinically, the first symptoms usually consist of a vague, dull pain in the lumbar region which may radiate into the groin. Gastrointestinal complaints of vomiting, diarrhea, anorexia, fatigue, and weight loss may occur. A few patients have complained of swelling of the legs. The main neurologic complaint is oliguria or anuria. On physical examination, one may palpate an enlarged tender kidney. Laboratory studies show little significant abnormality unless the obstruction is bilateral in which case an elevated blood urea nitrogen may occur.

Roentgenographic examination in the early stages may fail to disclose the nature of the disease. Positive roentgen findings are those of periureteral obstruction with displacement of the ureter toward the midline, hydronephrosis to the point of nonfunction, and occasionally some obliteration of the normal retroperitoneal fat lines. Such findings are suggestive and must be differentiated from other types of retroperitoneal neoplasm. The final diagnosis is confirmed only by biopsy and histologic study.

The authors recommend a long surgical excision extending from the xiphoid to the symphysis pubis. After immobilizing the right and left colon, the retroperitoneal periureteral structures can be exposed and ureterolysis can be performed. The patients are also treated with antibiotics and corticosteroids although there is little evidence that this medication is of any value. Recurrence of obstruction may develop. The disease should be recognized as a bilateral lesion and unilateral nephrectomy should be avoided. Spontaneous regression of the process is a possibility.

The authors present 1 table and 4 figures including pyelograms and histologic evidence of the nature of the disease.—*George W. Chamberlin, M.D.*

GENITOURINARY SYSTEM

AMPLATZ, KURT. Assessment of curable renovascular hypertension by radiographic techniques. Memorial Fund Lecture. *Radiology*, Nov., 1964, 83, 816-829. (From: Department of Radiology, University of Minnesota Hospitals, Minneapolis, Minn.)

During the past 10 years, there has been an increasing interest in the roentgenographic diagnosis of renovascular hypertension and the reported cure rate definitely justifies surgical repair in carefully selected patients. To aid in the careful selection of patients for surgery it is the author's purpose to emphasize two important roentgenographic techniques—aortography combined with pressure measurements and with the urea washout test—both of which assess physiologic alterations associated with curable renovascular hypertension.

The currently recognized curable types of unilateral renal lesions include arterial stenosis of the main renal artery or smaller arteries, segmental infarction, atrophic pyelonephritis, perirenal fibrosis, subcapsular hematoma, or renal artery aneurysms with partial

thrombosis. The common denominator of such a diverse group of lesions seems to be either a reduction in blood flow or decreased pulsations of the renal artery arborizations.

Aortography is a highly effective means of demonstrating anatomic lesions likely to produce renal hypertension, but it should be kept in mind that the above lesions may be found in normotensive patients and in those with essential hypertension. Therefore, the hemodynamic significance of renal artery narrowing is difficult to assess angiographically unless collateral vessels or a delayed flow of medium can be visualized. Any questionable area of narrowing should be assessed by pressure measurements, both distal and proximal to the area of narrowing with a gradient usually in excess of 40 mm. Hg in curable disease. The technique is described and its importance is exemplified by several cases of renal artery narrowing which were hemodynamically insignificant.

The important functional alterations in curable renovascular hypertension are a decreased flow of urine and hyperconcentration of the contrast medium on the involved side. This is the direct result of decreased vascular supply allowing a decreased rate of filtration and greater reabsorption of water and sodium. These functional characteristics are best visualized by intravenous pyelography and subsequently induced diuresis with a urea and saline solution. Several typical positive tests are presented and the rare false positive is discussed. The urea washout test is in essence a roentgenographic Howard test which should be a part of routine hypertension pyelography.

The author justifiably emphasizes that no longer can the vascular radiologist limit himself to the demonstration of vascular anatomy. The great goal of modern cardiovascular radiology lies not only in the exact demonstration of vascular anatomy but also in the assessment of hemodynamics and function.—*Edward B. Best, M.D.*

POSZVEK, H., and SEYSS, R. Zur Technik der Pyelographie. (The technique of pyelography.) *Röntgen Blätter*, Nov., 1964, 17, 493-499. (Address: Dr. med. H. Poszvek, Chir. Abtlg. des a. ö. Krankenhauses, Neunkirchen, Austria.)

The method employed by the authors is designed to provide more detailed information concerning the contours of the renal pelvis as well as the calyceal system than can be obtained by conventional urography. The technique is as follows:

1. A preliminary roentgenogram of the abdomen is taken.
2. Intravenous urography is performed in the usual manner.
3. Through a sterile syringe, 10 cc. of air (filtered through a 10 cm. thickness of absorbent cotton) is

injected into a ureteral catheter. Uniform distribution of the air throughout the renal pelvis is assured by altering the position of the patient from the Trendelenburg position to an erect position.

4. Fluoroscopic control is optional.

5. From 5 to 10 cc. of 20 per cent joduron is then injected into the renal pelvis.

In a case of acute pyelonephritis, intravenous urography showed some delay in filling of the collecting system and irregular contours of a slightly dilated renal pelvis. The retrograde, double contrast method demonstrated filling defects typical of papillary necrosis as well as tiny ulcerations and erosions of the mucosa of the renal pelvis.

Among the disadvantages of the method are that the air bubbles may lead to confusion, but experience will enable the examiner to clarify the situation. Only those tumors which are adjacent to the renal pelvis can be identified by the retrograde study. Calculi are better demonstrated in a pelvis filled with contrast medium.—*J. Zausner, M.D.*

FRIEDENBERG, MARVIN J., and CARLIN, M. RICHARD. The routine use of higher volumes of contrast material to improve intravenous urography. *Radiology*, Sept., 1964, 83, 405-413. (From: The Edward Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis 10, Mo.)

In a study to improve intravenous urography, the authors evaluated the routine use of higher volumes of contrast medium based upon the patient's body-surface area, instead of the routine 30 ml. currently used for all adults, regardless of size and weight. The quantity injected varied from 30 ml. for a body-surface of less than 1.30 m.² to 100 ml. for a body-surface area of over 2.40 m.² A total of 867 intravenous urographic examinations were performed in 787 patients. Eighty patients had both standard-volume and high-volume urography, thus serving as their own controls. No attempt was made to investigate the relative value of high volumes versus high concentration of contrast medium, nor a single versus divided doses.

The authors conclude that the use of higher volumes of contrast material improves the quality of intravenous urograms significantly. The frequency of excellent and good urograms is increased from about 65 per cent in standard-volume examinations to about 95 per cent in high-volume studies. The technique is justified, because it greatly increases the diagnostic accuracy of the examination and reduces the need for retrograde pyelography with its attendant hazards. The frequency of side-effects is slightly increased, but these are minimal in degree and well tolerated.—*Glenn W. Pett, M.D.*

ABRAMS, HERBERT L., BAUM, STANLEY, and STAMEY, THOMAS. Renal venous washout

time in renovascular hypertension. *Radiology*, Oct., 1964, 83, 597-609. (From: Department of Radiology, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, Calif.)

The conventional approaches to the problem of renovascular hypertension have included urography, isotope renography, renal arteriography, and split function studies. Herein is presented a study of the renal venous flow pattern in patients with hypertension which the authors choose to call the "washout time" and is defined as the total elapsed time from the onset of injection of contrast medium into the renal vein to its disappearance. Presented are the first 40 patients in whom cine renal venography was performed.

An Ödman yellow opaque polyethylene catheter, with a precurved tip, was placed in the right femoral vein percutaneously, advanced into the inferior vena cava and placed first in the left renal vein. Thereafter, 15 cc. of 76 per cent renografin was injected by hand or with a pressure injector in approximately three-quarters of a second and cinerecording on 35 mm. film obtained. Immediately following, the right kidney was studied in an identical fashion. The patients varied in age from 21 to 67 years with an average age of 45. Systolic blood pressures varied from 140 to 260 with the diastolic varying between 90 and 170. Urograms and arteriograms were obtained in all patients, and split function studies in 32. The cine renal venograms were compared with the arteriographic findings and with the renal plasma flow and glomerular filtration rate.

In patients without evidence of significant main renal artery obstruction, the renal venous washout time varied between 1.25 and 3.0 seconds. In only 1 case was it above 3 seconds when there was no evidence of stenosis of the main renal arteries, severe arteriolar nephrosclerosis, or diminished renal plasma flow. In a small number of cases without hypertension, studied for other reasons, renal venous washout times were comparable.

The renal venous washout time reflects the rate of blood flow through the kidney and is related to the presence of significant renal artery stenosis and to the renal plasma flow. With stenosis of less than 50 per cent, the average time was virtually the same as with no stenosis at all, *i.e.*, 2.3 seconds. With 50 to 80 per cent stenosis, the average washout time was above 3 seconds. When stenosis of 80 per cent or more was present, the average washout time was 8.1 seconds, and no time less than 6 seconds was noted. Differences in washout times between the two kidneys correlated well with differences in urine production and para-amino-hippuric acid concentration.

Therefore, the renal venous washout time furnishes supporting evidence of the importance of a stenotic lesion of a renal artery in hypertension, and the extent to which it is of dynamic significance. With

significant renal artery stenosis and reduction in renal blood flow, the washout time is usually prolonged. In the absence of significant renal artery stenosis, the washout time may be prolonged when there is profound arteriolar nephrosclerosis and a consequent diminution in renal plasma flow. The application of renal cine venography to the clarification of operability of a stenotic lesion as well as the limitations of the technique are discussed and illustrated.—Howard R. Stewart, M.D.

SAINT-YVES, IAN F. M. Problems associated with the diagnosis of solitary kidney: congenital or acquired? *Brit. J. Urol.*, Sept., 1964, 36, 347-353. (Address: Angau General Hospital, Lae, New Guinea.)

The incidence of congenital, solitary kidney varies from 1:500 to 1:1,500 according to different authors. The sex incidence is almost equal. There is a distinct predominance of renal agenesis on the left side. Failure in development presents with an absence of the kidney and ureter on the affected side, usually with associated nondevelopment of the ipsilateral side of the trigone of the bladder. There is absence of the adrenal gland in approximately 25 per cent of cases.

Renal agenesis must be differentiated from: (1) renal aplasia, in which the ureter is present in whole or in part; (2) crossed, fused renal ectopia; and (3) unilateral renal atrophy.

In each of the 3 cases presented, there was non-function of the left kidney by intravenous pyelography and there was poor definition of the renal outline. The classic cystoscopic appearance was absence of the bladder trigone on the affected side and absence of the ureteric orifice. In 1 case, aortography revealed absence of renal arteries on the affected side. The solitary, functioning kidney showed compensatory hypertrophy. A case of marked atrophy of the kidney secondary to tuberculosis is presented to illustrate the problems in differential diagnosis.—David Corbett, M.D.

LINDNER, A., and SCHRAMM, W. Renal calyceal diverticula: their importance in the differential diagnosis of renal disease. *German Med. Monthly*, Oct., 1964, 9, 414-416. (Address: Dr. A. Lindner, Urologische Abteilung des Allgemeinen Krankenhauses, Hagen, Germany.)

Calyceal diverticula of the kidney are defined by the authors as hollow spaces in the general parenchyma lined by transitional epithelium, which have their own supply of collecting tubules and communicate with the renal calyx through a fine connecting channel. On the pyelogram they appear sharply defined, smooth-walled, containing deposits of contrast medium, often with a fine channel connecting them to the calyx. They must be differentiated from

a solitary cyst of the kidney, which on a pyelogram usually does not fill with contrast material.

Hydrocalyx and tuberculous cavitation also enter into the differential diagnosis. In hydrocalyx, the calyx itself is enlarged, whereas in calyceal diverticula the calyx is of normal size and shape. Tuberculous cavities are often irregular and blurred in outline in contrast to calyceal diverticula which are sharply defined and smooth in contour. Tuberculous cavities also exhibit delayed and uneven filling. Examination of the urine usually helps in the differentiation; while normal in calyceal diverticula, it shows pyuria, albuminuria, and often microscopic and gross hematuria in the presence of tuberculous cavities. Cultures and animal inoculations provide the final answer.

Calyceal diverticula generally do not produce any referable symptoms, except when concretions form in their lumen, giving rise to diverticular colic. They are almost always an incidental finding, usually diagnosed during a routine pyelographic study.

The authors add 8 of their own cases to the literature, stressing the fact that this entity should not be misdiagnosed as renal tuberculosis.—*Kenneth M. Nowicki, M.D.*

RILEY, J. M., and HANAFEE, W. Transaxillary renal angiography. *J. Urol.*, Aug., 1964, 92, 148-152. (From: Department of Radiology, University of California Center for the Health Sciences, Los Angeles, Calif.)

Percutaneous transfemoral arterial catheterization for the demonstration of the renal arteries is a commonly used technique because of its ease of performance, reliability, and low incidence of complications. However, in a small number of cases an alternate approach is desirable particularly in those individuals who have occlusive disease of the iliac vessels or aorta with or without aneurysms. In these instances, the authors recommend the use of percutaneous catheterization of the left axillary artery since occlusive disease of the upper extremities is much less common than in the lower extremities.

The left axillary artery is punctured high in the axilla and the Seldinger needle is inserted. This is slightly more difficult than femoral puncture, but it is easier than brachial artery puncture at the elbow. The left axillary artery is used because it is difficult to catheterize the descending aorta from the right side. A flexible guide is introduced under image intensified fluoroscopic control and an attempt made to pass the guide wire into the descending thoracic aorta. In instances in which this cannot be accomplished, the left shoulder is elevated and abducted. A two-catheter system is employed. One is a small polyethylene curved-end catheter which is inserted into a larger straight-end polyethylene catheter. In cases in which the guide wire does not pass readily into the descending aorta, the catheters are inserted

over the guide and are passed to the aortic arch. With the guide wire slightly withdrawn, the curved end of the smaller inner catheter is then directed posteriorly and guided into the descending aorta. This is usually accomplished best with the patient in the left anterior oblique position. After the guide and the inner curved catheter have been removed, the end of the larger catheter is placed at the level of the 2nd lumbar vertebra. This catheter has an end hole and three side holes. Radiopaque substance is then injected with a pressure of 5 kg. per cm.². Injection is done while the patient is performing the Valsalva maneuver. It is important to check the position of the end of the catheter before injection to make sure that it is not in one of the branches of the aorta. In some instances selective renal arteriography may be performed by re-inserting the small curved catheter and placing it in the orifice of the renal artery. In such instances, recordings of arterial pressures and gradients may be taken. Serial roentgenograms may be made in the erect or horizontal posture and various positions as indicated.

Following removal of the catheters, it is important to apply pressure over the brachial artery for at least 15 minutes without suppressing the radial pulse. The patient should then keep the arm motionless for at least 3 hours and with restricted motion for 24 hours. Vigorous motion of the upper extremity should be avoided for several days. A hematoma occurring at the site of the needle puncture is more common with this procedure than it is with femoral punctures and in some instances may represent a serious complication.

The authors include 8 figures to illustrate the value of this procedure.—*George W. Chamberlin, M.D.*

WEIDNER, WILLIAM, RILEY, JOHN, and HANAFEE, WILLIAM. Angiographic evaluation in renal transplantation. *Radiology*, Oct., 1964, 83, 579-586. (From: Department of Radiology, UCLA Center for the Health Sciences, Los Angeles, Calif. 90024.)

The authors emphasize the role of angiography in selecting potential kidney donors and evaluating recipients before and after renal transplantation. Unsuspected vascular abnormalities in the donor or recipient can require modification of the surgical procedure or rejection of a prospective donor.

Angiography techniques of examination can be divided into three groups: aortography for prospective donors, vena cavography for the candidates for renal transplantation and pelvic arteriography in the postoperative period to visualize the arterial anastomosis in the recipient. Aortography was performed by the percutaneous technique via the femoral or left axillary artery, using a double catheter. Pressure injection of 35 cc. of 75 per cent hypaque was made with the Gidlund injector at 5 kg./cm.² Films were exposed at a rate of 3 per second for 2 seconds, 1 per

second for 3 seconds, and a delayed film at 10 seconds. Developmental variations, fibromuscular hyperplasia, renal artery stenosis, renal artery aneurysm and atheromatous plaque formation at the ostium of the renal artery may be detected.

Vena cavography was also performed by the percutaneous catheter technique, whenever the recipient gave a history of recurrent thrombophlebitis or occlusive venous disease in the lower extremities. Bilateral simultaneous injections were done to delineate the pelvic veins more clearly than a single injection, using a larger catheter with a higher pressure. Selective renal venography was carried out where renal artery thrombosis was a possibility in the recipient.

Eighteen renal transplantations were performed at the University of California Center for the Health Sciences at Los Angeles since 1957. Some of the problems encountered in the donated kidneys include multiple renal arteries, small renal arteries, early bifurcation of single renal arteries and fibromuscular hyperplasia. Recipients of transplants have had problems such as atheromatous disease in the internal iliac artery, pelvic endophlebitis, and anomalies of the pelvic veins.

Multiple renal arteries were found in 23.8 per cent of the subjects studied angiographically and the anatomic incidence of multiple renal veins was 14.4 per cent. Angiographically, the average lengths of the left and right renal arteries were 42 and 47 mm., respectively, with a range of 18 to 130 mm. The minimal acceptable length of the renal artery for successful anastomosis has been set at 20 mm.

Occasionally, preoperative aortography may be indicated in the recipient, particularly if there is any evidence of aorto-iliac disease. Postoperative pelvic arteriography is sometimes necessary to evaluate the arterial anastomosis.—*A. W. Sommer, M.D.*

BERES, JOSEPH A., ZBORALSKE, F. FRANK, WILSON, STUART D., and AMBERG, JOHN R. Percutaneous transrenal venography in experimental renal vein obstruction and human renal vein thrombosis. *Radiology*, Oct., 1964, 83, 587-596. (From: Divisions of Medicine and Radiology, Milwaukee County Hospital, Milwaukee 13, Wis.)

This report attempts to set forth the experimental basis for the development and application of percutaneous transrenal venography. The renal venous circulation, including collateral drainage, is reviewed and correlated with the venographic observations of partial and complete renal vein occlusion.

Fifteen dogs were studied in various stages of unilateral renal vein occlusion utilizing the renal approach as described by Muehrcke. The technique for this study employs a 15-gauge Rochester plastic needle, 5 cc. 50 per cent sodium diatrizoate, and a

serial film changer. The tip of the needle is placed into the renal parenchyma.

Renal vein occlusion, partial or complete, causes vascular engorgement and permits opacification of the renal and/or perirenal venous complex. Therefore, the site of renal vein occlusion and/or collateral venous circulation is demonstrated. Even though the renal vein should not be opacified, the demonstration of tortuous and dilated collateral vein(s) is evidence of renal vein thrombosis. It was also noted that aspiration of blood is difficult in the absence of increased venous pressure and injection of the contrast medium, therefore, is directly into the parenchyma. Direct injection into renal parenchyma does not appear unduly hazardous, resorption is prompt, and a histologic review shows only minimal localized and organized fibrosis. Caution is indicated, however, against larger volume and excessive pressure injections to avoid rupturing a swollen kidney. The value of a pre-examination excretory pyelogram, and particularly the retrograde pyelogram, is emphasized.

The case records of 2 patients in whom percutaneous transrenal venography was performed are presented. Results in each case correlated positively with the operative findings.

The contraindications for this procedure appear to be limited to a bleeding tendency and sensitivity to the contrast material.—*John Bond, M.D.*

GARNETT, E. S. A trial of the radioisotope renogram. *Brit. J. Urol.*, Sept., 1964, 36, 332-339. (From: Department of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London, England.)

The author begins with a discussion of the interpretation of the normal hippuran 131 renogram. The first phase is explained by rapid accumulation of hippuran by the tubule cells and its transfer into the tubule lumen. The importance of tubular uptake and transfer in this phase has been confirmed by several experimental studies. The second phase represents continued tubular accumulation of hippuran, the slope of the curve being less than in the first phase because of the fall in hippuran concentration in the blood after the first minute. The peak of the renogram depends on 4 factors: (1) renal blood flow which determines the rate at which the isotope is presented to the nephrons, (2) the number of functioning nephrons, (3) the ability of the nephrons to transport the isotope, and (4) the rate of elimination of the isotope from the nephrons. The third phase begins when the rate of elimination of the isotope from the tubules exceeds the rate of accumulation. The slope of the phase depends on several factors including blood flow and the patency of the ureters.

The experimental portion of the article consists of correlations of blood flow, measured by endogenous creatinine clearance, as related to the ratio of the height of the tracing 12 minutes after injection to the

peak height of the tracing. Results showed a significant relationship between the ratio (rate of fall of the third phase of the renogram) and the rate of clearance of creatinine. The rate of fall was shown to be an inverse linear function of the clearance rate. Since the clearance rate reflects blood flow, the results strongly suggest that the rate of fall of the third phase is also a function of the renal blood flow.

Twenty-seven hypertensive patients were studied using the renography. The results compared with another study showed that 22 per cent of patients with normal renograms were proved to have unilateral renal disease; 41 renograms on normotensive patients showed 28 per cent false positive results.

It is concluded that the renogram is of little value as a screening test for unilateral renal disease.—*William K. Littman, M.D.*

SIGMAN, EUGENE M., BENDER, MERRILL, and BLAU, MONTE. Radiohippuran renography and radiohippuran renal autofluoroscopy. *J. Urol.*, Aug., 1964, 92, 153-158. (From: Department of Urology, Buffalo General Hospital and Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo, N. Y.)

A new isotope procedure, renal autofluoroscopy, is presented in this article.

The autofluoroscope is a non-scanning device designed to give a graphic representation of the distribution of gamma emitting isotopes within the

human body. It incorporates such features as collimation with a good depth response and adequate resolution, high efficiency, and a high contrast data presentation system. Instead of a single sodium iodide crystal, the autofluoroscope uses 293 sodium iodide crystals packed in a 6×9 inch arrangement. The collimator provides a single tapered aperture for each crystal. Twelve 3 inch multiplier phototubes are separated from the crystal bank by a 4 inch thick lucite light pipe. Gamma ray activity occurring in any crystal is represented as a dot of light in the corresponding locations on the face of an oscilloscope. When the autofluoroscope is monitoring renal tissue that is in the process of clearing a labeled compound such as hippuran I^{131} , the flashes of light that will appear on the oscilloscope screen will bear a direct spacial relationship to the segment of renal tissue that originally produced the source of gamma energy. When such a system is applied to a single intravenous dose of hippuran I^{131} , a radiohippuran excretory urogram is obtained. This will differentially demonstrate cortical activity, medullary activity, and collecting system activity so that the radiohippuran excretory urogram may be expressed graphically as a compartmental fractional analysis.

By using this method in conjunction with standard radiohippuran renography, the authors have studied normal patients with dehydration versus water diuresis, chronic pyelonephritis, hypertension, hydronephrosis, and tubular necrosis. Ten figures illustrate the value of this method.—*George W. Chamberlin, M.D.*





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ECHOENCEPHALOGRAPHY*

By RAY A. BRINKER, M.D.,† DONALD L. KING, CAPT. USAF, M.C.,‡ and
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ECHOENCEPHALOGRAPHY is the term coined by Leksell¹⁴ in 1956 for a new technique by which the position of the midline structures of the brain can be determined. The technique involves passing a beam of pulsed ultrasound into the head in the temporoparietal region and recording the returning echoes. The midline structures, usually the lateral walls of the third ventricle but also the septum pellucidum, pineal gland and interhemispheric fissure, send forth the strongest and most easily recognizable echoes which can then be used to determine the presence or absence of a displacement of these structures. This technique, used increasingly in Europe since 1956, has in the past 2 years come into use in some medical centers in the United States. It is an extremely useful neurologic screening test, as significant as detection of a calcified pineal gland on a

frontal skull roentgenogram, and yet obtainable in over 99 per cent of patients. It is the purpose of the authors to describe the technique of echoencephalography and add the results of our clinical trial to the already convincing body of data in the literature indicating the value, efficiency, and accuracy of the procedure.

The determination of the midline echo is of value in all patients, especially those without a calcified pineal body, suspected of having neurologic disease. In almost every case where echoencephalography is desired, routine skull roentgenograms are also obtained at the same time, the former supplementing the latter. Use of the equipment and performance of the test are easily learned, and there is no doubt that neurologists, neurologic surgeons, and radiologists, as well as other specialists, will find it of value. It is useful as a screening

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The views expressed herein are those of the authors and do not necessarily reflect the views of the US Air Force or the Department of Defense.

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method for lateralizing pathology, selecting the appropriate neurooentgenologic procedure, and following the clinical course of patients. Echoencephalography may also be very valuable in patients with head trauma, especially children, for checking the position of the midline structures on admission and subsequently for detecting any shift that might occur due to the development of subdural hematoma.

HISTORIC REVIEW

The first use of ultrasound to determine the position of the midline structures of the brain was reported by Leksell¹³ in 1955. As early as 1942 and 1947, Dussik *et al.*^{3,4} had reported on the application of continuous transmitted ultrasound to central nervous system diagnosis. In 1950, French, Wild and Neal⁶ reported the detection of cerebral tumors in postmortem material by use of a pulse-echo technique. It was Leksell, however, who found that, by placing the ultrasonic transducer on the temporal region, one could record echoes from the midline structures and determine their position with relative ease on the intact skull. In 1956, he described the basic technique¹⁴ and presented several case reports. In 1958,¹⁵ he stressed the role of the pineal body as a source of the midline echo. In 1959, De Vieger and Ridder² and Jefferson⁹ reported their early experiences. Lithander,^{16,17,18} in 1960 and 1961, contributed significantly to the technique of echoencephalography with the description of the transmission signal as a simple method of control. Others, including Jeppsson,^{11,12} Taylor *et al.*,²⁰ and Jefferson,¹⁰ have contributed reports on clinical trials and discussions of the technique, source, and accuracy of the midline echo. Ford and Ambrose⁵ have recently reported the largest series of cases to date in which the accuracy and validity of the technique is well documented.

PRINCIPLES

Ultrasound is defined as high frequency, greater than 20,000 cycles per second,

wave-form mechanical energy which requires some type of medium, usually liquid or solid, for its propagation. It thus differs fundamentally from electromagnetic radiation. Because of its high frequency, usually on the order of 1 to 2 million cycles per second, it has many properties similar to light. It can be reflected, refracted, absorbed, and dispersed. In the soft tissues of the body, it has a velocity of approximately 1,500 meters per second. Discussions of the physics of ultrasound can be found in the works of Jeppsson,¹² Carlin,¹ Goldman and Huter,⁷ and Richardson.¹⁹

In echoencephalography, the most important property of ultrasound is its reflection from tissue surfaces or interfaces. A portion of the sound beam will be reflected when it passes from one conducting medium to another, such as from the gray matter to the cerebrospinal fluid. The portion of the sound beam reflected is proportional to the difference between the specific acoustic impedance of the two mediums. The specific acoustic impedance of a tissue is defined as the product of its density and the velocity of the sound within it. The second critical factor influencing the portion of sound energy reflected and the usable portion of the echo which is to be recorded is the angle of the incident beam to the tissue interface. The closer the angle of incidence is to normal, the greater is the portion reflected, and similarly the greater the portion that can be recorded. When the angle of the reflected sound beam differs from the angle of the incident beam by more than a few degrees, the energy of the returning signal is markedly reduced and, therefore, less likely to be recorded. The third important factor determining the strength of the returning signal is the surface area upon which the incident beam strikes. The greater the area, the greater will be the amplitude of the returning signal.

Ultrasound is generated in short wave-trains or pulses by a specially constructed transducer made of a very thin ceramic crystal. When a voltage is placed across the

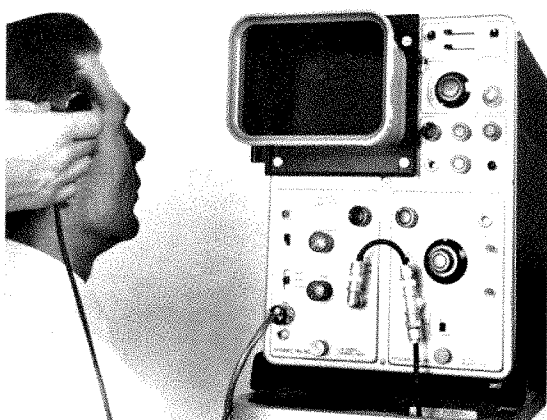


FIG. 1. Echoencephalograph in use on a patient.
Note the transducer position above the ear.

crystal, it changes its thickness according to the piezoelectric effect and vibrates for a few cycles, creating a short wave-train or pulse of high frequency waves. Conversely, when returning echoes strike the transducer, they mechanically vibrate the crystal, setting up a very small potential difference across its surface. This signal can then be amplified and electronically manipulated.

EQUIPMENT

The equipment used* in echoencephalography (Fig. 1) consists basically of a timing mechanism, a pulser, a transducer, a sweep circuit, an amplifier, an oscilloscope, and a camera. The timer activates simultaneously the pulser and the sweep circuit. The pulser instantaneously places a voltage across the transducer, producing a pulse of ultrasound. At the same instant the horizontal sweep begins moving from left to right across the face of the oscilloscope. This sweep has been calibrated so that a known distance on the oscilloscope screen corresponds to a known distance in the head. When a returning echo is recorded by the transducer, the signal is amplified and displayed as an upward deflection of the horizontal sweep. When a satisfactory recording has been obtained, it is photo-

graphed with the oscilloscope camera. The process of pulsing the transducer is repeated 360 times per second. The length of time that the transducer is actively producing ultrasound for each pulse is on the order of 5 microseconds. Thus the transducer is in a receiving state, listening for returning echoes more than 99 per cent of the time.

METHOD OF EXAMINATION

The method of examination of a patient consists of recording the midline echo from the right and left temporal regions at a point just above and slightly anterior to the pinna of the ear corresponding to the thin portion of the squamous temporal bone (Fig. 1). In addition, after completion of this, a control transmission signal is recorded, utilizing two transducers placed in the same location. These three measurements are photographed on a single film with the transmission signal uppermost, the recording from the right in the mid-portion with the deflection upwards, and the recording from the left slightly below and with the deflection downward (Fig. 2).

Recognition of the midline echo cannot logically depend upon its position on the baseline but must rest upon other characteristics. It is usually the strongest signal

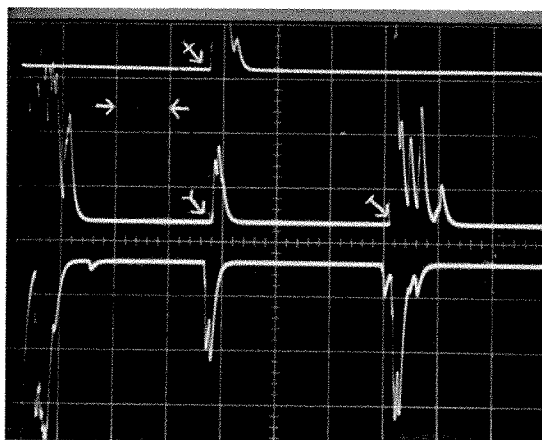


FIG. 2. Normal echoencephalogram (confirmed).
 →← 2 cm. of tissue
 +→ Transmission signal
 >→ Midline echo on the right
 <→ Left inner table as seen from the right

* VT-400 Echoencephalograph. Physionic Engineering, Inc., Longmont, Colorado.

arising from the central portion of the trace. When the tracing is normal or there is only a slight displacement of the midline structures, it will often be notched or double in appearance. The midline echo can often be recognized from the symmetric distribution of other echoes about it. Pulsation is often noted in the midline echo; however, this is not a reliable sign as other pulsatile echoes can be seen. When the transducer is rocked slightly it usually appears as the most dominant and persistent signal. Another important factor in recognition of the midline echo is its relationship to the control transmission signal. This signal is an ultrasonic measurement of the diameter of the head between the two points from which the right and left determinations were made. This diameter is equal to the distance from the transducer to the midsagittal plane and back again, providing there is no head asymmetry. Thus it represents a theoretic prediction of the location of the midline echo. If the midline structures are undisplaced, the midline echoes from both sides of the head and the transmission signal should all line up evenly on the oscilloscope. If there is a displacement of the midline structures and the procedure has been correctly done, the midline echoes should shift away from the transmission signal equally in opposite directions. As a final criterion for an adequate examination, the back-echoes should line up equidistant from the transducer, assuring, as nearly as possible, that the two sound paths were coincident.

CASE MATERIAL

Four hundred and sixty-nine echoencephalograms from patients who were examined at the Neurological Institute, Columbia-Presbyterian Medical Center were reviewed. Each patient was examined at the request of his physician or prior to a special neuroradiologic examination by a technician trained in the technique of midline echoencephalography. Each examination was then checked by one of the authors. Each patient was examined prior to other study when it was possible, and

usually 24 hours before cerebral angiography or pneumography. The patients' ages ranged from infancy to elderly and their conditions included all types of neurologic disorders, congenital, vascular, neoplastic, and traumatic.

METHOD OF ANALYSIS

Each echoencephalogram was graded as being either normal; namely, the midline structures were within 2 mm. of the midline, or as showing a displacement, the direction and degree of which were stated. Subsequently, the patients' roentgenograms were reviewed and measured to determine the presence or absence of midline structure displacement and to quantitate it. All measurements on the roentgenograms were made in the posteroanterior projection usually to the outer tables of the skull. The pineal gland was measured from the center of the visible calcification. The anterior cerebral artery was measured from its medial margin in its proximal portion as well as in its distal (upper) portion. The medial aspect of the internal cerebral vein was measured from its anterior third just posterior to the foramen of Monro and from its posterior third as determined in the frontal projection with the aid of the lateral view. The anterior third ventricle was measured from its midplane as demonstrated in the brow-up projection as was the septum pellucidum. The posterior third ventricle was measured from its midplane as demonstrated in the brow-down projection. All measurements were made to the nearest millimeter. No case was considered confirmed unless one or more of these measurements was obtained with exception of those cases which had operative confirmation only, or those which had demonstrated unequivocal lesions roentgenographically to account for the findings but in which the deep veins were not filled, or the vessels were so distorted as to make measurement impossible. These cases were considered qualitatively confirmed. The midline echo was considered normal if it was within 2 mm. of the midplane. The roentgenographically demonstrated mid-

line structures were considered normal if they were within 2.5 mm. of the midplane for the pineal gland, third ventricle, and posterior internal cerebral vein, and within 3 mm. of the midplane for the anterior cerebral-pericallosal artery. In addition to placing each case in the appropriate group, a comparison of the quantitative measurement of the shift of the midline echo with the displacement of each of the measured structures on the roentgenograms was made on cases correctly predicted in which displacement of the midline structures was present. The mean difference between the midline echo and each measured point was determined.

RESULTS

The data are presented by groups in Table I. A total of 469 cases were examined. Of these 287 were confirmed, 180 were unconfirmed, and in 2 cases an acceptable examination could not be performed. Of the cases correctly predicted, there were 204 with undisplaced midline structures, 51 with displaced midline structures, and 24 in which the midline echo and the pineal gland, posterior third ventricle, or posterior third of the internal cerebral vein were within 2 mm. of the midplane although the more anterior structures were abnormal in position. Of the incorrectly predicted cases, there was 1 with displaced midline structures, 1 in which the direction of the displacement was reversed, and 6 with undisplaced midline structures.

Of the 287 confirmed cases, in 279 or 97.2 per cent correct predictions were made regarding the presence or absence of midline structure displacement, and, if present, the direction of the displacement. Of those cases in which the posterior third ventricle, posterior internal cerebral vein, or pineal gland were in normal position (234 cases), 97.4 per cent were correctly predicted. Of the cases in which these structures were abnormal in position (53 cases), 96.1 per cent were correctly predicted. Of the cases in which the midline echo was interpreted as normal (229 cases), 99.5 per cent were correct predictions giving a false

TABLE I
SUMMARIZED DATA

Confirmed Cases		
Correctly Predicted		279
Undisplaced Midline Structures	204	
Displaced Midline Structures	51	
Undisplaced Posteriorly, Displaced Anteriorly	24	
Incorrectly Predicted		8
False Positive	6	
False Negative	1	
Reversal of Displacement	1	
Normal Midline Echo, Total		229
Correctly Determined	228	
Incorrectly Determined	1	
Abnormal Midline Echo, Total		58
Correctly Determined	51	
Incorrectly Determined	7	
Total Cases Confirmed		287
Unconfirmed Cases		
Total Cases Unconfirmed		180
Undisplaced Midline Echo	173	
Displaced Midline Echo	7	
No Echo Obtainable		2
Total Cases Examined		469

negative rate of 0.5 per cent. Of the cases in which the midline echo was interpreted as abnormal (58 cases), 87.9 per cent were correct predictions giving a false positive rate of 12.1 per cent. These results are summarized in Table II.

In Table III are listed the mean differences between the displaced midline echo and the measured displacement of the various structures on the roentgenograms. The measured displacement of the midline echo differed from that of the pineal gland on the average of 1 mm., the posterior internal cerebral vein 1.09 mm., the posterior third ventricle 1.20 mm., and from all three considered together 1.15 mm. The distribution of the differences between the midline echo and the various structures is illustrated in Figures 3 through 10.

TABLE II
SUMMARIZED RESULTS

Confirmed Cases Correctly Predicted	
Total	97.2%
Undisplaced Posterior Structures	97.4%
Displaced Posterior Structures	96.1%
Confirmed Cases Incorrectly Predicted	
False Negative	0.5%
False Positive	12.1%

CASE ILLUSTRATIONS

Figures 11 through 16 are echoencephalograms and appropriate roentgenograms from the neuroroentgenographic studies, with brief case summaries, showing the usefulness and applicability of echoencephalography in clinical, neurologic and surgical practice.

DISCUSSION

An accuracy of prediction of 97.2 per cent is comparable to the results reported by other authors. Ford and Ambrose⁵ in their large series had an over-all accuracy rate of 93.8 per cent and on their last 300 cases an accuracy rate of 96.8 per cent. They had a false negative rate of 4.3 per cent and a false positive rate of 9.2 per cent as compared to our rates of 0.5 per cent and 12.1 per cent. Lithander¹⁸ reported an over-

TABLE III
CORRELATION OF MIDLINE ECHO AND
MIDLINE STRUCTURES

Differences between the Midline Echo and	Mean (mm.)
Pineal Gland, Posterior Third Ventricle, and Posterior Internal Cerebral Vein	1.15
Pineal Gland	1.00
Posterior Internal Cerebral Vein	1.09
Posterior Third Ventricle	1.20
Anterior Third Ventricle	2.55
Anterior Internal Cerebral Vein	2.65
Anterior Cerebral Artery	3.43
Pericallosal Artery	3.83
Septum Pellucidum	2.00

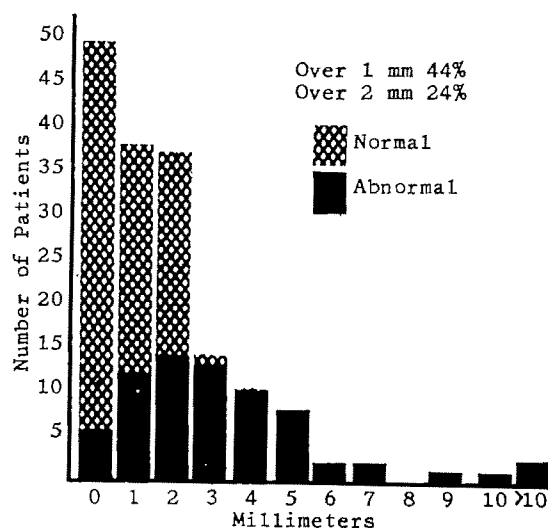


FIG. 3. Difference between the anterior portion of the anterior cerebral artery and the echo. (Note: Figure 3 to 10 represents quantitative relation between the measured structure and the echo. In each case the echo was subtracted from the position of the structure as measured on the roentgenograms. Normal means lack of any midline shift over 2 mm. in the roentgenograms.)

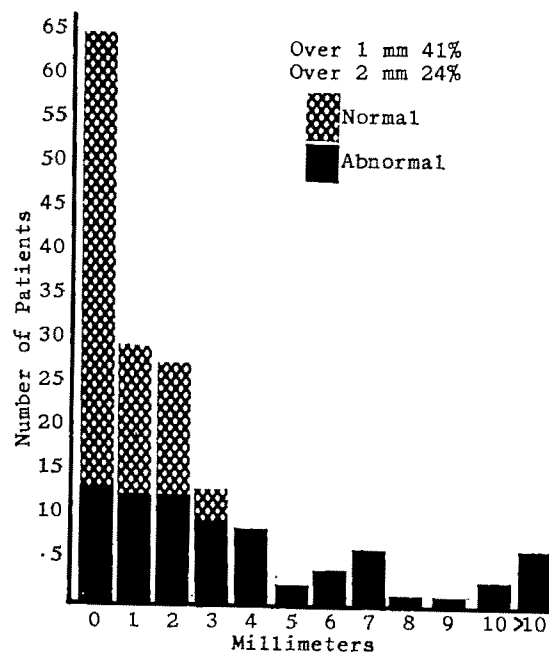


FIG. 4. Difference between the posterior portion of the anterior cerebral artery and the echo.

all accuracy rate for 275 cases of 94.2 per cent with 6 per cent false positive and 5.7 per cent false negative.

An analysis of our errors reveals that the one false negative result occurred in a patient with a marked hydrocephalus and marked shift of the midline structures due to a large arachnoid cyst. Possibly in this case another strong reflecting structure such as a wall of the lateral ventricle actually lay in the midplane. In one case there was a reversal of the shift. This was probably due to recording the upper trace from the left side of the head contrary to the usual procedure, and then failing to correct for this in the interpretation. In another case early in the series, the examiner was misled into expecting a shift, and may have been too greatly influenced by the clinical history. Another error was due to the use of excessive amplification resulting in too confusing a pattern of signals. Two errors were due to unrecognized skull asymmetry, one in a postoperative patient. One case was

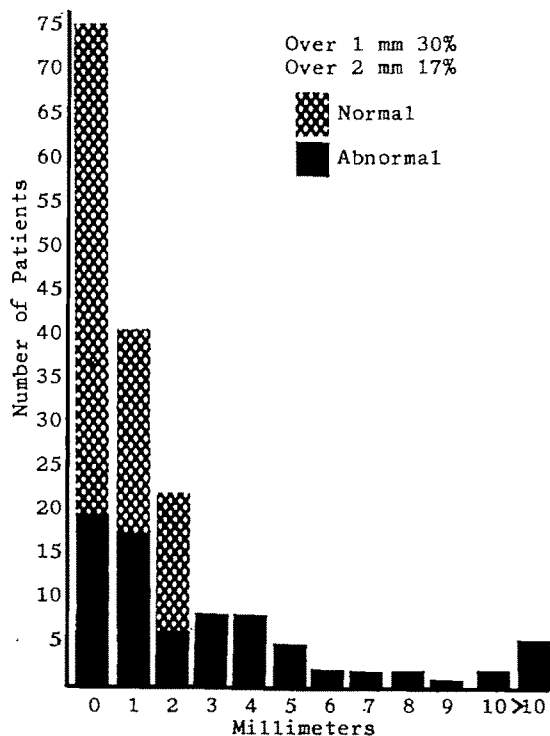


FIG. 5. Difference between the anterior portion of the internal cerebral vein and the echo.

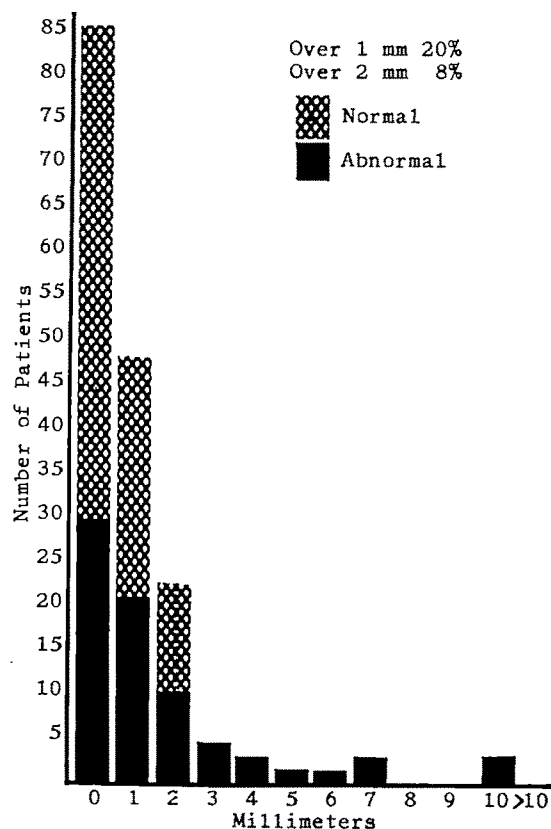


FIG. 6. Difference between the posterior portion of the internal cerebral vein and the echo.

due to the presence of hydrocephalus in which one wall of the third ventricle, recorded from both sides of the head, was thought to represent a displaced midline. The hydrocephalus was not recognized. A subsequent echoencephalogram demonstrated no displacement. The last error was due to the diagnosis of hydrocephalus

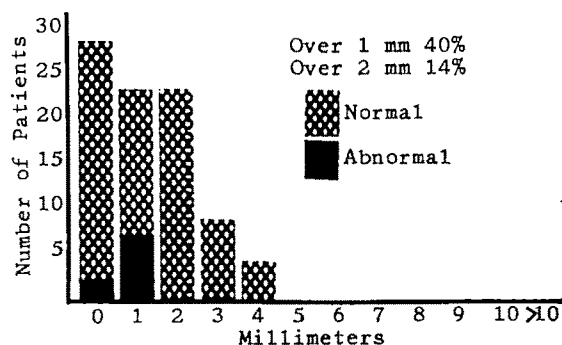


FIG. 7. Difference between the septum pellucidum and the echo.

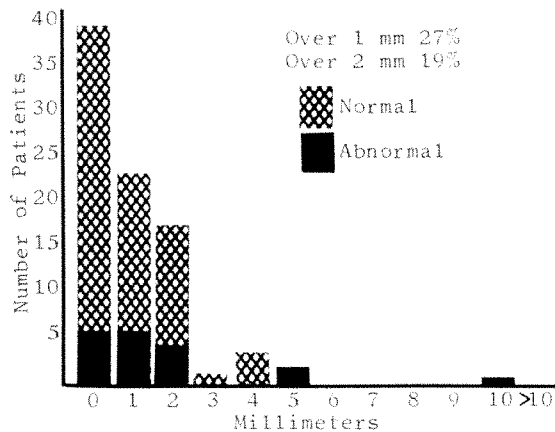


FIG. 8. Difference between the anterior third ventricle and the echo.

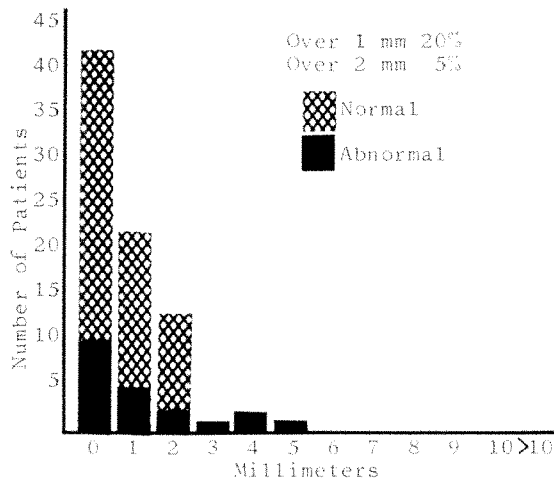
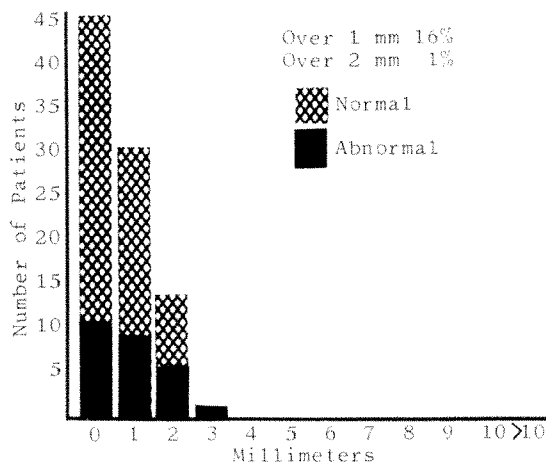


FIG. 9. Difference between the posterior portion of the third ventricle and the echo.



which was not present. In this case the midline structures and midline echo were normal in position, but it is nevertheless considered an error of interpretation. The 7 unconfirmed cases of abnormal midline echoes consisted of 3 postoperative cases with previously demonstrated abnormalities, 2 cases which could not be confirmed because of clerical error, and 1 case which



FIG. 11. Case 1. The echoencephalogram demonstrates a 4 mm. displacement of the midline structures to the right. The bizarre echoes in the first portion of the left hand trace may have been produced by the intracerebral hematoma.

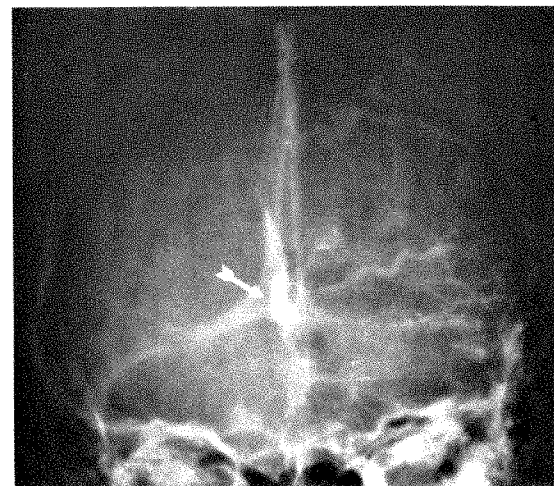


FIG. 12. Case 1. Venous phase of left carotid angiogram shows the internal cerebral vein to be shifted to the right. The shift of the posterior portion of the vein is 5 mm.



FIG. 10. Difference between the calcified pineal gland and the echo.

was not studied by special neuroradiologic procedure.

The higher correlation of the displaced midline echo with the position of the more posteriorly situated structures is not unexpected and reflects the positioning of the transducer on the head. The implication of this is that the posterior portion of the third ventricle may be normal in position, and

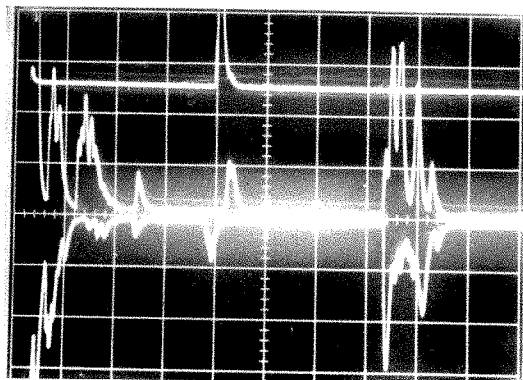


FIG. 13. Case 2. The midline echo is displaced 4 mm. to the left. Note the notched appearance of the midline echoes, the symmetry of the midline echoes, the symmetry of the displacement in relationship to the transmission signal, and the equidistant back-echoes.

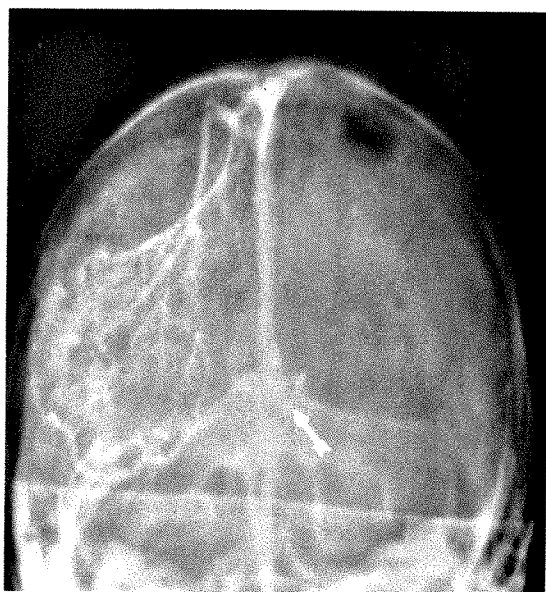


FIG. 14. Case 2. A large high parietal convexity hematoma is demonstrated in the venous phase of right carotid angiography. The posterior portion of the vein was shifted 5 mm. to the left of the midline.



FIG. 15. Case 3. The echoencephalogram shows no evidence of displacement of the midline structures. The midline echoes from both the right and the left are within 2 mm. of the transmission signal and the back-echoes are equidistant.

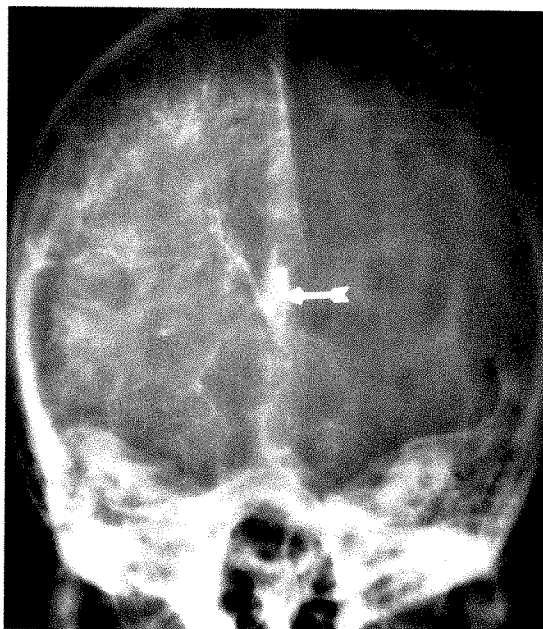


FIG. 16. Case 3. The right carotid angiogram demonstrates a space-occupying mass deeply situated in the anterior suprasylvian region, producing a 3 mm. displacement of the anterior portion of the internal cerebral vein. The posterior portion of the vein (arrow) was in the midline by measurement and thus confirmed the echoencephalographic finding. This case is an example of displacement anteriorly in the presence of normal posterior structures, and illustrates the incapability of current techniques to detect small anterior displacements.

therefore the midline echo undisplaced, even in the presence of a marked shift frontally. The data indicate the accuracy of the midline echo measurement in most cases. Most of the large differences between the midline echo and the posterior structures occurred in cases that had a marked displacement. Over 90 per cent of the differences between the midline echo and the posterior structures were 2 mm. or less.

SUMMARY

Four hundred and sixty-nine echoencephalograms were reviewed in which 287 were confirmed by special neuroroentgenologic procedures. Anatomic correlation was then undertaken between structures measured on the roentgenograms and the echoes. The over-all accuracy of prediction of the posterior midline structures was 97.2 per cent. The false negative rate was 0.5 per cent and the false positive rate was 12.1 per cent.

Echoencephalography is an easy, rapid, and apparently harmless neurologic screening test. It carries the same clinical significance in routine use that the demonstration of a calcified pineal gland does when seen on the frontal roentgenogram of the skull. It is obtainable on almost every patient and is especially useful in screening patients suspected of having a space-occupying intracranial lesion.

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MEDICAL ULTRASONICS*

ESSENTIALS OF ECHOENCEPHALOGRAPHY

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ULTRASONIC echo sounding is at present being used in several diagnostic fields of medicine. Among these are studies of the mitral valve, eye disturbances, kidney and ureteral stones, breast cancer, fetal cephalometry and other intra-abdominal conditions.

Our experience with ultrasonic echo techniques so far has been limited to studies of intracranial lesions. In addition to presenting our experience with echoencephalography, the aim of this report is to discuss some basic principles of ultrasound as an introduction to those interested in this subject.

BACKGROUND AND PRINCIPLES

When mechanical pressure or tension is applied to the surface of certain crystals such as quartz, Rochelle salt or barium titanate, an electric voltage is generated. This phenomenon was discovered in 1880 by the brothers P. and J. Curie³ and named "piezo-electric effect." In 1881, Lippmann predicted the reverse effect: when electric charges are applied to the surfaces of such crystals, the crystals will expand or contract depending on the signs of the charges. This latter phenomenon is termed the "reverse piezo-electric effect."

If an alternating voltage is applied to such a crystal, a reverse piezo-electric effect will result in vibration of the crystal. This vibration will be most pronounced when the frequency of the alternating voltage coincides with the natural mechanical or resonant frequency of the crystal. Vibration of the crystal will then generate sound waves in the surrounding media. If the frequency of those sound waves is above 20,000 cycles per second, they are outside

the normal hearing range and are termed ultrasonic sound waves.

These principles of ultrasound generation were first applied by Langevin⁶ when he was commissioned by the French government during the First World War to find a means of locating enemy submarines which at the time were attacking French vessels. His patent proposed an assembly of mosaic quartz crystals cemented between steel plates to be used for generation and reception of ultrasonic waves. The device was not employed to any extent because of imperfections usually attendant with the development of new devices.

During this period, Nicholson⁹ of the Bell Laboratories in America did pioneer work with Rochelle salt crystals. Subsequently, quartz and other piezo-electric crystals and ceramics became the basis of many underwater detecting and signaling devices.

During the Second World War, new methods such as Asdic and Sonar were perfected and widely used for anti-submarine warfare with great success. Although there are several methods of generating ultrasonic waves for various purposes, the simplest one most commonly used in medicine is that employing crystal transducers, not unlike those used in underwater Sonar detection equipment.

In practice, a piezo-electric crystal or transducer is momentarily excited by pulses of high frequency current and the resultant expanding and contracting movements are transmitted to a fluid. These vibrations or sound waves in the fluid travel until they collide with any surface or interface of a different medium. The resulting echo travels back and hits the crystal, thus generating an electric signal which can then be

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amplified and displayed by various means including oscilloscopy. While ultrasound is more easily propagated through liquids or solids than through gas, it is otherwise similar to light in many respects insofar as it can be directed in straight beams which can be reflected and refracted.

The characteristic that determines the amount of attenuation and reflection of the waves is known as the *specific acoustic impedance* and this is related to the density and elasticity of the medium. When a wave traveling through one medium impinges on a boundary between it and a second medium of different acoustic impedance, part of the energy continues traveling forward through the second medium while the remainder is reflected back into the first medium. The amount of energy reflected back is dependent on the differences in acoustic impedance of the two media. Strong reflections are obtained at boundaries between liquids and air. Under these conditions, the energy which continues traveling forward through the second medium will be greatly diminished.

Reflections are not limited to the first interface. The energy which continues traveling forward beyond the first boundary will be again partly reflected at the next boundary. Thus it is possible to obtain echoes from several succeeding boundaries. It must be kept in mind, however, that each succeeding echo will be greatly attenuated because only part of the energy is transmitted through a boundary and because the reflected wave must pass twice through each preceding boundary—once in each direction of travel.

Another factor which must be kept in mind is that a very regular interface may act as a reflector and a beam may be reflected away at an angle, in the same manner as a beam of light is reflected by a mirror.

The echo sounding method thus consists basically in transmitting a short pulse of ultrasonic sound into the medium being examined and detecting any echoes that are reflected back from interfaces lying in the

path of the original wave. The elapsed time between the transmitted pulse and the received echoes is a measure of the depth or distance to the interfaces (Fig. 1).

Although strong reflections take place when transmitting from liquid to solid, the usual way of getting ultrasonic waves into a solid is by using thin films of liquids as couplants, since the air boundaries reflect almost 100 per cent of the energy.

The entire process of transmission of the pulse and detection of returning echoes takes place in only a fraction of the thousandth of a second. The process can thus be repeated many times per second to provide a display which appears stationary to the observer.²

DISPLAY METHODS

One of the simplest methods of presenting the information from the returning echoes is by means of an oscilloscope. The spot of light on the face of the cathode ray screen can be controlled in three independ-

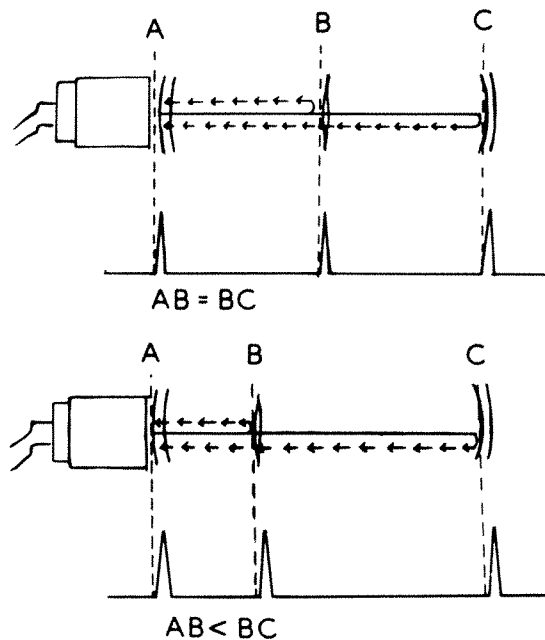


FIG. 1. When the midline structures are not displaced, the midline echo is equidistant from both sides of the skull, *i.e.*, $AB = BC$. Displacement of the midline causes differences between AB and BC , as seen in the lower half of the illustration.

ent or simultaneous ways: horizontally, vertically or by change of brightness.

Usually, horizontal displacement represents elapsed time between the transmitted pulse and the received echoes. This, therefore, is a measure of the depth or distance to the interface, assuming that the speed of sound in the soft tissues is constant. The observed patterns appear stationary on the screen due to repetition many times per second of the process of transmission and reception.

The signals of ultrasonic echoes displayed in other ways take their nomenclature from the terminology of radar as follows:

1. *Amplitude Modulation or Mode A.* In this mode, the intensity of the trace is kept constant. The returning echoes, converted into electrical signals, are made to displace the trace in the vertical direction. The amount of vertical displacement thus represents the strength of the echo and the horizontal distance represents the depth or distance to the reflecting boundary.

The primary use of this display mode is to determine the distance or depth to the reflecting boundary. An additional use is the study of structures such as tumors having more than one component of different density or elasticity (Fig. 2).

2. *Intensity Modulation or Mode B.* In this display, the trace of returning echoes varies with intensity. The echoes are thus presented as bright dots of light along the horizontal, the intensity of the dots representing the strength of the echoes and the distance between dots representing depths.

If the target possesses a component of motion in the direction of the ultrasonic

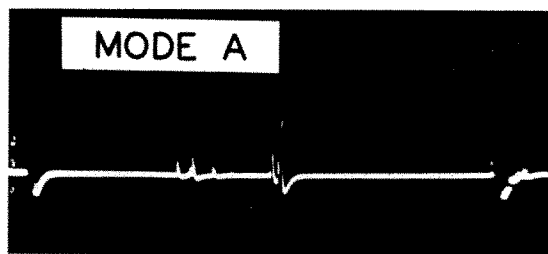


FIG. 2. In Mode A display, the amount of vertical displacement represents the strength of the echo.

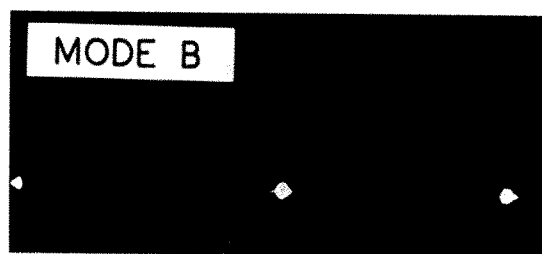


FIG. 3. In Mode B display, the intensity of the dots represents the strength of the echo. In both Modes A and B, the separations between spikes and dots represent distance.

beam, displacement of the dots will occur. If a slow vertical sweep is incorporated in the oscilloscope, these displacements can then be recorded (Fig. 3).

3. *B-Scan.* By mounting the probe on a linear synchronized scanning device, pictorial representations of structures can be obtained. The principle of the formation of these two-dimensional pictures by scanning was described by Newell⁸ (1963), who compared ultrasonic echoes with laminagraphy. These are really composite pictures formed from a large number of one-dimensional pictures. The structural representations compare quite accurately with anatomic cross-sections.

A variant of the linear scan can be obtained by mounting the probe on a device animated by an angular fan-like sector movement.

Table I shows a summary of the different ways in which the ultrasonic echo information may be displayed on the oscilloscope.

4. *Other Display and Measurement Methods.* In addition to the oscilloscope, readout displays can also be made on stripcharts, recorders or photographic film. Digital counters may be used with great accuracy to measure elapsed time between transmitted pulse and received echoes. The intensity of the transmitted signal and its attenuation may also be used as a measurement parameter if a second transducer is used for receiving pulses passed through the structure.

Another approach, introduced by Yoshida *et al.*¹⁴ (1961), is to use a continuous

TABLE I
SUMMARY OF OSCILLOSCOPIC DISPLAY METHODS

Mode	Horizontal Distance	Vertical Distance	Intensity
A	Depth (time)	Strength of echo	Constant
B	Depth (time)	Constant	Strength of echo
B with Vertical Sweep	Depth (time)	Time	Strength of echo
B-Scan	Depth (time)	Positions of transducer during scan	Strength of echo

beam of ultrasound instead of repeated pulses, recording the Doppler effect. The change in frequency that takes place when the target has motion towards or away from the transducer can be displayed as a signal on the oscilloscope and provides another measurement parameter. Although the time occurrence of intermittent motion may be determined by this method, it does not indicate the position of the reflecting surface in relation to the transducer.

BEHAVIOR OF ULTRASOUND IN SOFT TISSUE

In practice, ultrasound can be considered to propagate in a straight line in soft tissue and can thus be used to examine those targets in the path of its transmission. Soft tissues of the body may be visualized by ultrasound without the use of contrast media with a resolution approaching that of the gross anatomic appearance. Radio-lucent materials can be detected despite the presence of blood or other soft tissue in the immediate vicinity. Since echoes are produced by discontinuities in acoustic impedance, a change in elasticity is equally as effective in the production of an echo as a change in density. This allows differentiation of soft tissues even if they are of the same density provided they are of different elasticity, a characteristic unlike any other known visualization technique. Thus, an artery produces a strong echo because it has an elasticity different than surrounding tissue.

The speed of transmission of ultrasound through soft tissue is in general almost equal to its velocity in water at the same

temperature; namely, 1,500 meters/sec. Small variations in speed are related to variations in local temperature or composition.

The resolving power of ultrasound is inversely related to its wave length. The shorter wave lengths give the highest resolution but have the lowest penetrating power. The longer wave lengths have lower resolution but higher penetrating power. The wave length is related to the frequency of the ultrasound by the following simple formula:

$$\text{Wave length} = \frac{\text{speed of sound in the medium}}{\text{frequency}}$$

Table II gives the wave lengths corresponding to the frequencies most commonly used in diagnostic echo-sounding.

The average power levels used in diagnostic ultrasound range approximately between 1/1,000 to 1/100 of those used for therapeutic mechanical or thermal effects. The diagnostic value of ultrasound does not depend on producing any physiological effects. It depends more on the body's effect on ultrasound than on ultrasound's

TABLE II
RELATIONSHIP OF FREQUENCY AND WAVE LENGTH
OF ULTRASOUND IN SOFT TISSUE

Frequency	Wave Length in Soft Tissue
0.5 mc.	3 mm.
1 mc.	1.5 mm.
2.5 mc.	0.6 mm.
5 mc.	0.3 mm.
10 mc.	0.15 mm.

effect on the body. No observable damage to tissues has been reported with the use of pulsating ultrasound for diagnosis.

ECHOENCEPHALOGRAPHY

The bulk of work on the brain has been confined principally to A-Scope presentation. Ultrasonic frequencies of 1.5–2.5 mc./sec. have been found appropriate for A-Scope presentations of midline studies. The essential information rendered is the position of brain midline structures which act as a reflecting boundary. Any conditions that tend to produce a lateral displacement of midline structures will alter the position of the echo from each side. The two echoes, one obtained from the right and the other from the left will therefore fail to line up in the midline as traced on the oscilloscope. Measuring the distances from the leading edges to the two echoes and dividing by two, the degree and side of displacement can be determined, assuming the skull to be symmetrical. The accepted limit of normal displacement of the midline echo is less than 3 mm. Therefore, displacements of 3 mm. or more are considered abnormal.

Another display method may be obtained by counting the time elapsed from each side to the midline, subtracting one from the other. Dividing by two gives the displacement, considering that ultrasonic waves penetrate brain tissue of 1 cm. in 13 microseconds.

By counting the time required for transmission between one wall and the other, or the degree of attenuation, some information can be deduced about tissue composition, local temperature and degree of hydration (edema), considering that all three factors affect the transmission of ultrasound.

Linear B-Scan and its variant, angular or sector fan-like scans, are also useful for obtaining cross-sectional views of tumors and other lesions. The thickness and curved shape of the skull, however, add difficulties to these presentations.

Tumor echo patterns have been sought by some workers. Gliomas generally have

irregular and continuous echoes while the echoes of meningiomas and metastases seem to be isolated and sharp. The technique used in these cases may necessitate shaving the hair of the skull, osteoplastic trepanation through the dura mater and direct application of a special probe on the surface of the brain after opening the dura. Insertion of a special miniature transducer into the brain tissue, as proposed by Tanaka *et al.*,¹³ presents a new means of locating tumors deep in the brain and merits further investigation.

Our technique for obtaining midline echoes is as follows: the probe is placed firmly against the side of the patient's head, just above and as near the ear as possible. By moving the probe gently from front to back and up and down, strong midline and far wall echoes will appear. It is necessary to use a couplant such as ordinary degassed tap water to avoid air boundaries or bubbles between the probe and the skin surface (Fig. 4).

Apparatus provided with double traces permits checking the absence of differences in delay of the transmitted pulse ("main Bang") and the far wall echoes on both traces, right to left and left to right. Both traces should line up as mirror images even if it is necessary that the probe be repositioned many times before the study is confirmed.

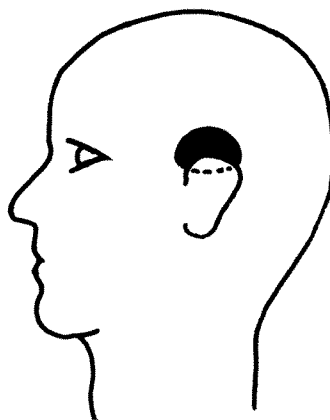


FIG. 4. Transducer is placed above ear as indicated by area in black.

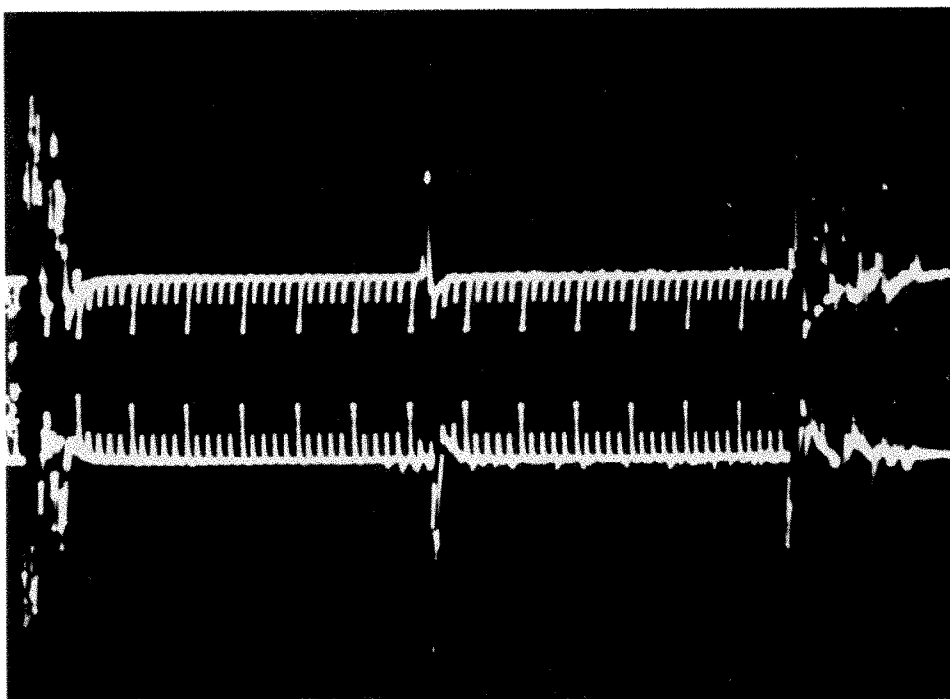


FIG. 5. Normal echogram. The vertical deflections of both traces from right to left and from left to right are displaced less than 3 mm. from the midline.

ECHO IDENTIFICATION

Three groups of echoes are displayed on the oscilloscope screen in midline measurement and must be accurately identified (Fig. 5).¹⁰

Group I. The first group is composed of echoes from the near surface of the skull, inner and outer bony tables, and meningo-brain interface. To be recognized is the main spike which represents the echo from the outer table of the skull and the second spike representing the inner table. A third spike, separated from the second by 3 or 4 mm. and reduced in height, is sometimes seen corresponding to the meningo-brain boundary (Fig. 6).

Lack of good coupling or the presence of foreign material interposed between the transducer and the skull will produce many echoes, varying in location and strength. These echoes can extend as far as the midline of the brain, making the trace unreadable (Fig. 7).

Group II. The second group of far wall

echoes has been recently studied in detail by Smyth.¹¹ He points out that this group of echoes should contain one due to the skin-to-air interface in order to provide evidence that the sound beams from both sides are traveling similar paths and that these paths are closely perpendicular to the midline structures. According to this procedure, the far wall group of echoes should include at least three and usually four spikes (Fig. 8).

The presence of echoes B, C and D is essential for interpretation of the trace. Smyth believes that the A echo assumes great importance for localization and

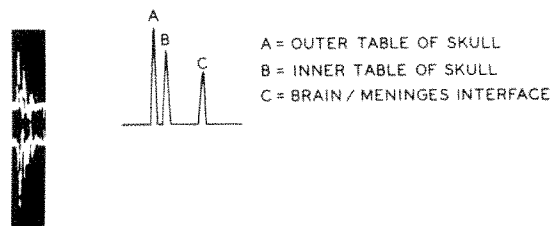


FIG. 6. Pattern of near wall echoes.

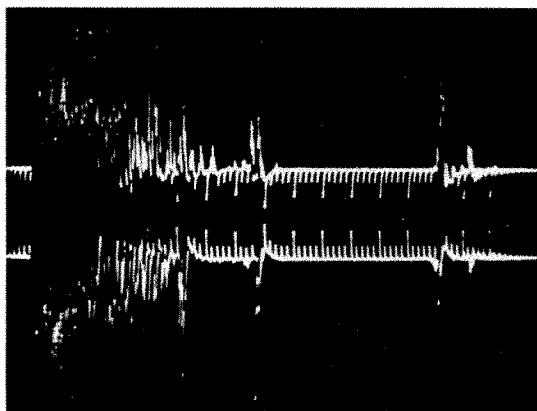


FIG. 7. Foreign material between transducer and the skin can result in echo deformity extending almost to midline.

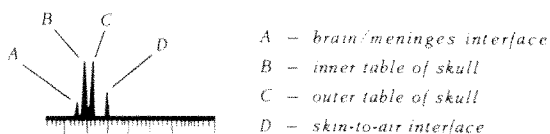


FIG. 8. Pattern of far wall echoes.

measurement of subdural hematomas. Positive identification of the skin-to-air interface can be made by rubbing or pressing a finger against the skin in an area over the far wall diametrically opposite the transducer.

Group III. Midline echoes. Although there is still some disagreement about which particular structure causes the midline echo, there is little question now about the usefulness of diagnosing the presence and approximate location of space occupying

lesions by shifts of these echoes. It is believed that the midline echoes are most likely produced by the falx cerebri, inferior sagittal sinus, septum pellucidum, the third ventricle and pineal complex.^{1,5}

Despite the existence of different structures in the midline, the path of the ultrasonic beam will ordinarily cross only one of them.

Various difficulties arise in the interpretation of these echoes. The following criteria can serve for purposes of identification: (1) the midline echo always produces a prominent spike; (2) its shape seems to approximate the letter M when expanded; (3) it frequently pulsates as it crosses a large artery or the choroid plexus of the third ventricle; (4) its base is broad; and (5) sometimes two spikes are present. These distinguishing features can best be observed when the trace is expanded horizontally on the viewing screen (Fig. 9, *A*, *B* and *C*).

The most frequent causes of complete and persistent absence of midline echoes are excessive attenuation by undue thickness of the skull wall and dispersal of the ultrasonic beam and echo by irregularities of both the near and far internal skull boundaries.

Erroneous measurements in symmetrical skulls are usually due to misinterpretation of echoes produced by structures that are not situated in the midline. Infratentorial areas and anterior portions of the frontal

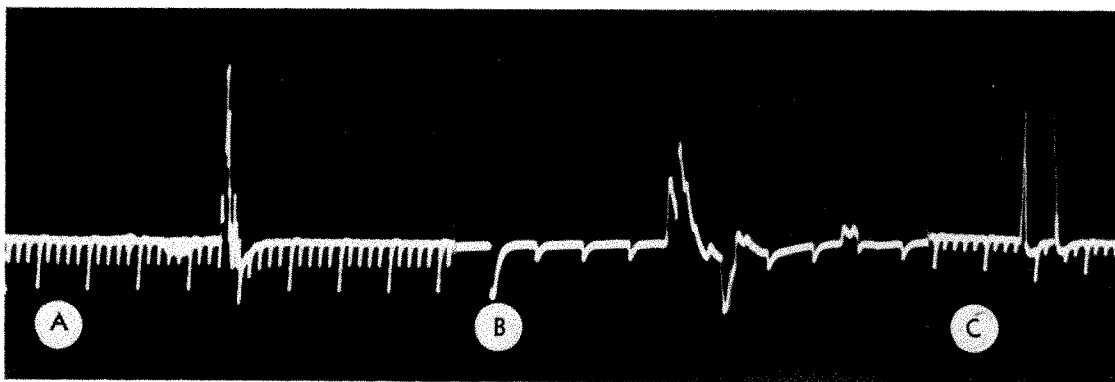


FIG. 9. Midline echoes. (*A*) Normal unexpanded trace. (*B*) M-shaped spike due to expanded trace. (*C*) Midline echo with two spikes.

lobes are difficult to examine because of the low position of the former and the absence of dominant midline structures in the latter.

Other echoes caused by structures not in the midline sometimes appear on traces. One of the most important is the echo produced by the wall of the lateral ventricle. This echo can easily be mistaken for one in the midline. In hydrocephaly, this echo appears closer to the skull wall.⁴

Tumors and other lesions produce abnormal echoes which are very difficult to identify. In order to lessen the effect of perturbing echoes, transducers shaped to focus the ultrasonic beam at the depth of interest are being investigated.¹² When using these, however, one must be aware that the energy level at the focal point is much greater than that of unfocused transducers and so the factor of safety is reduced.

RESULTS

Echogenic midline measurements performed at Albert Einstein Medical Center on 155 adult individuals have been analyzed; of these, 124 were selected and 31 rejected either because a satisfactory follow-up was not obtainable or because operative or postmortem confirmation was not available. Only in one instance was it impossible to obtain a satisfactory midline echo.

Thirty-four studies were done on healthy adults with no intracranial symptoms or other diseases. The maximum displacement obtained was 2 mm. in 2 cases. In the remainder, the displacement varied from 0 to 1.5 mm.

Of 9 proved primary intracranial tumors, 7 presented a displacement of 3 mm. or more. In 2 cases, the midline echo was within normal limits. One of these had a voluminous glioblastoma multiforme which was operated on the previous year with considerable herniation of the tumor through an extensive craniectomy. The far wall echo could not be obtained from the side of the craniectomy. The other pa-

tient presented a moderate sized pituitary chromophobe adenoma and its midline echo was not displaced. All the intracranial tumors with echo displacement also had positive angiographic evidence of tumor.

In 2 cases, repeated measurements after 2 month intervals disclosed increased displacement paralleling the general deterioration of the patient.

In 1 case of meningioma of the greater wing of the sphenoid with an initial displacement of 3 mm., the echo receded to the midline 42 days after the completion of Co⁶⁰ therapy.

Among 5 metastatic intracranial tumors, 4 presented a displacement of 3 mm. or more and the midline echo was normal in 1 case.

Sixteen cases of suspected intracranial tumors showed no displacement and other studies confirmed the absence of tumors.

Among 11 cases of recent or old cranial trauma, 10 revealed no midline displacement. In the 11th case, an initial displacement of 6 mm. improved with recovery of the patient, the echo receding to the midline within 4 days (Fig. 10, *A* and *B*).

In a group of 20 patients with ill-defined neurologic pathology and vague symptoms, a displacement of 3 mm. in one case was later found to be due to an old left subdural hematoma.

In 4 cases of subdural, subarachnoid, or intracerebral hematoma later confirmed by operation or autopsy, the midline echo had various shifts ranging from 4 to 9.4 mm. (Fig. 11 and 12).

Among 25 cases of thrombosis of the internal carotid artery or its main branches, 22 revealed no displacement. In 3, displacement ranged from 3 to 4 mm.

In all cases, the direction of shift in the echograms coincided with the confirmed displacement. The amount of displacement obtained by echogram is not always the same as reported by angiography. The entire course of the anterior or pericallosal cerebral artery is revealed in angiograms, while only a small target area sit-

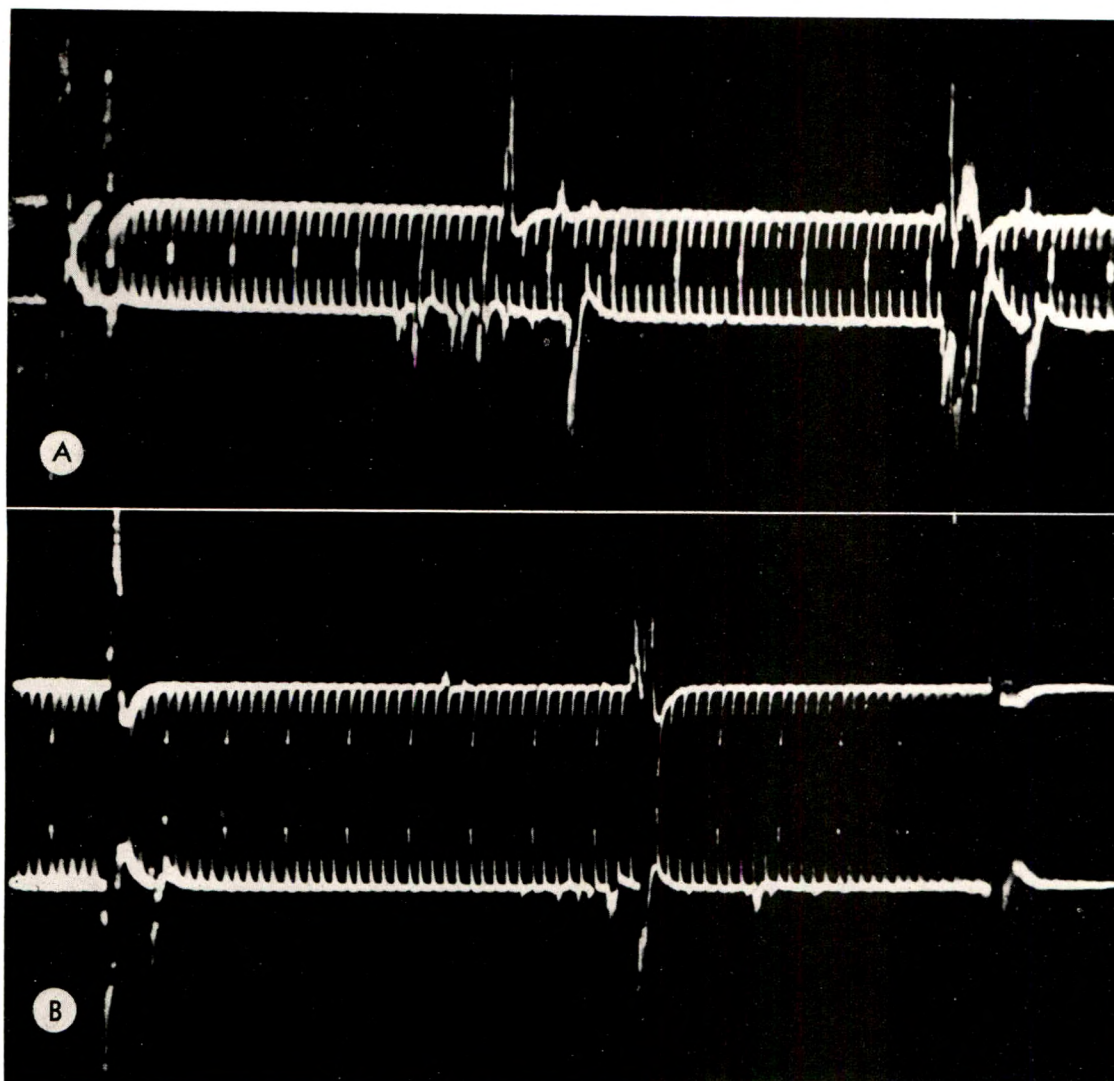


FIG. 10. Severe head trauma. (A) Upper echogram; midline echo shifted 6 mm. to the right.
(B) Lower echogram 3 days later; midline echo has receded to normal position.

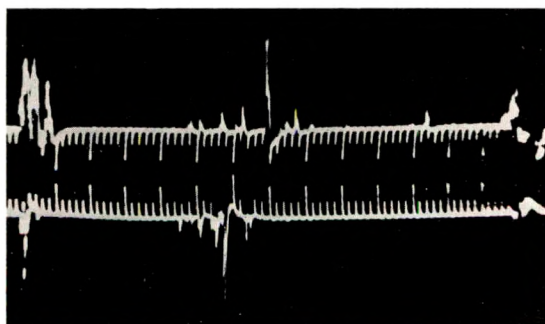


FIG. 11. Right-sided subdural hematoma (autopsy); 5 mm. left displacement of midline echo.

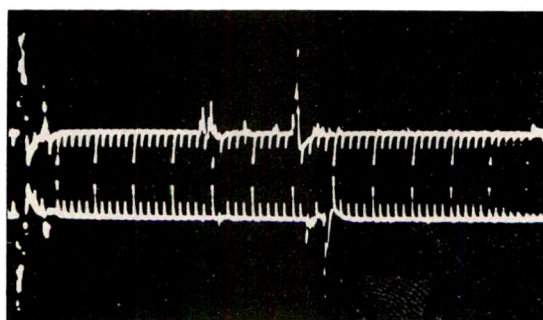


FIG. 12. Left-sided cerebral infarct (autopsy); 4 mm. right displacement of midline echo.

uated somewhat more posteriorly and less easily displaced is exhibited in the echogram; and these differences account for the discrepancies between the two diagnostic methods. The discrepancy is least when the position of the internal cerebral vein is chosen for reference instead of the anterior cerebral artery.

For purposes of standardization, midline echo determinations should be compared whenever possible with: (1) the anterior cerebral or pericallosal artery for lesions situated in frontal regions; (2) the internal cerebral vein for the medial regions; and (3) the pineal body for slightly more caudal areas (Fig. 13 through 15, inclusive).⁷

DISCUSSION

Our initial experience is too limited to permit conclusions, but we have yet to encounter a true displacement of the vascular cerebral structures not detected by the echogram. Conversely, cases found to have an echographic shift were confirmed later by angiography. Furthermore, never have we had a disagreement between echographic and angiographic findings. Nevertheless, it has always been our policy for safety's sake to confirm midline displacement by repeated examinations. The painless, quick and safe determination of midline structure shifts by echography is impressive. The presence of space-occupying lesions in the supratentorial part of the brain can be readily indicated except when bilateral lesions are present not associated with midline displacement.

Echoencephalography is not a substitute for other diagnostic methods. When a midline shift is found, confirmation by angiography seems advisable except in cases of severe head trauma or other conditions in comatose patients presenting clear clinical signs of compression with no lateralizing signs. In such instances, if an increasing shift is revealed by repeated echograms, surgical interference may become warranted.

SUMMARY

Ultrasonic echo sounding is at present being used in diagnostic medicine in several fields. This presentation is concerned principally with ultrasonic measurement of brain midline displacement.

By sending an ultrasonic beam through the skull, it is possible to obtain the reflected echo of the midline brain structures. The location of this echo depends on the distance between these structures and the lateral wall of the skull. Any condition that tends to displace the midline structures will displace the position of the echo. Even cerebro-atrophic processes can be detected by measuring the third ventricle width, while in hydrocephalus, it is possible

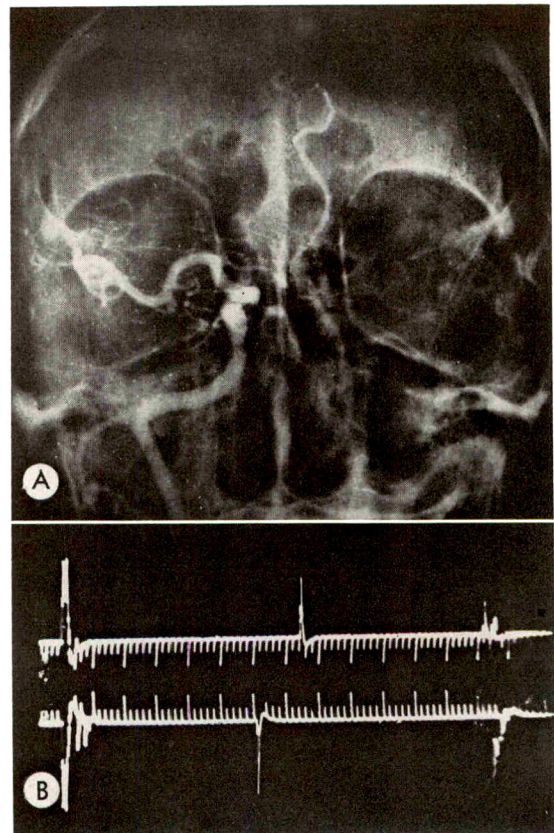


FIG. 13. Right-sided glioblastoma multiforme (biopsy). (A) Left displacement of the anterior cerebral artery. (B) Midline echo displaced 7 mm. to the left.

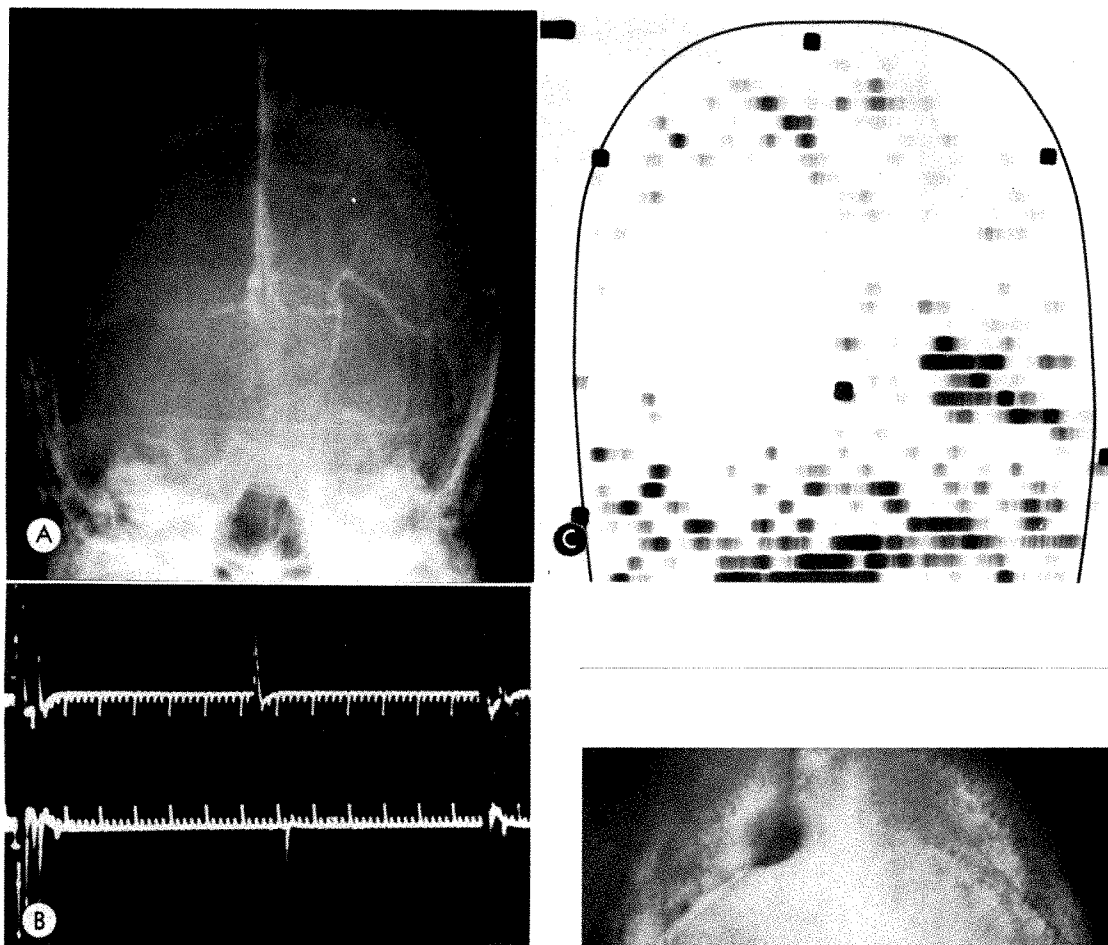


FIG. 14. Left-sided glioblastoma multiforme: (A) Venogram; internal cerebral vein displaced to the right. (B) Four mm. right displacement of midline echo. (C) Brain scan showing location of tumor stain.

to determine the thickness of the remaining cerebral layer or the expanded inferior horn of the lateral ventricle.

One hundred and fifty-five patients have been examined by echoencephalography in the last 11 months. These include healthy patients and those with tumors,

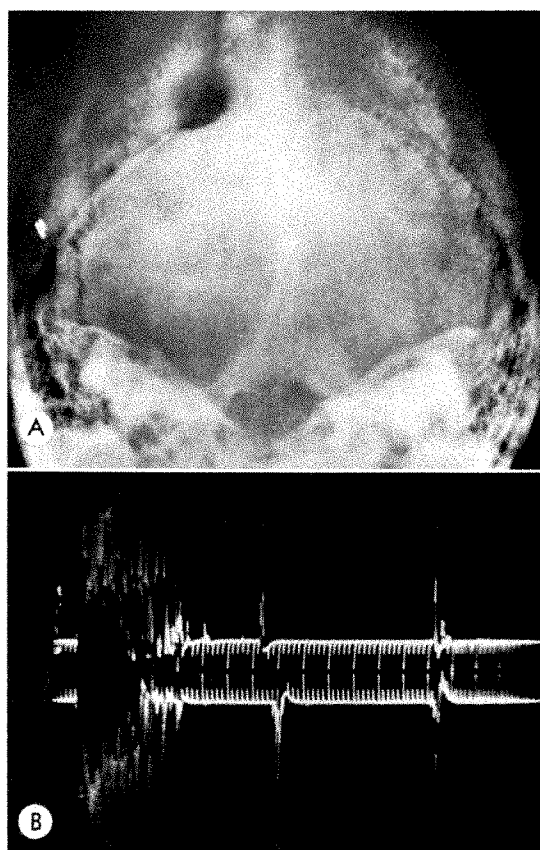


FIG. 15. Left-sided recurring glioblastoma multiforme (biopsy). (A) Right displacement of the pineal. (B) Four mm. right displacement of midline echo.

intracranial metastases, cranial traumas, hematomas and cerebral thrombosis. All cases of confirmed midline shifts were detected by echography.

Echoencephalography is not a substitute for other diagnostic methods; it is, however, an easy and atraumatic way of providing evidence of midline displacement, thus indicating the presence of space-occupying lesions.

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ECHOENCEPHALOGRAPHY IN GENERAL HOSPITAL PRACTICE

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ECHOENCEPHALOGRAPHY is the term which has been applied to the use of ultrasonics in determining the location of various structures within the skull, particularly the position of the midline. The use of a beam of pulsed ultrasound for this purpose was first reported in 1955 by Leksell.⁸ Several additional reports on this method have appeared in the medical literature since that time.^{4,11,13} Most of these have come from centers specializing in the treatment of neurologic diseases. The present report is designed to present the results of 723 echoencephalographic examinations and to evaluate the place of echoencephalography in a general hospital situation. The patients studied were all referred for radiographic examinations of the skull because of neurologic disease, trauma, otologic problems, or medical conditions with possible associated intracranial changes.

Ultrasonics refers to sound which has a frequency of over 20,000 cycles per second. The ultrasonic waves are produced by electrical stimulation of a piezo-electric crystal which acts as a transmitter and receiver. Rapid voltage variations are produced by a high frequency generator which causes the production of bursts of ultrasonic pulses. These last for only a fraction of a second followed by a relatively long "dead-time." During this interval the crystal or transducer acts as a receiver for reflected ultrasonic pulses. The incoming pulses are then converted to electric potential variations which can be presented on a cathode-ray oscilloscope. The deflections produced in this manner, are, in this examination, presented in a display perpendicular to the linear time sweep of the oscilloscope. The distance of the deflections from the initial pulse created by the edge of the transducer is related to the time necessary for the ultrasonic waves to travel from the crystal to

the point of reflection and back to the transducer. Ultrasonic waves travel at varying speeds in different solid and liquid media. The waves interact with matter by absorption, reflection, refraction and diffraction. At an interface between substances of varying acoustic impedance, some of the ultrasound waves will be reflected directly back along their initial course and picked up by the transducer. The proportion acting in this manner depends upon the specific acoustic impedance at the interface and the angle at which the beam strikes the interface.

The intensity of the ultrasonic beam used for this examination is extremely low, approximating 0.0005 to 0.02 watts per square centimeter. Considerable experimental work on animals using this level of power has not shown any detectable damage or teratogenic effect to date.¹⁴

The equipment used in all of our cases has an operating frequency of 2.25 megacycles.* The transducer is a barium titanate crystal with a flat applicator surface measuring 1.9 cm. in diameter.

METHOD OF EXAMINATION

Evaluation of the location of the midline structures within the skull by echoencephalography is ordinarily a rapid, simple examination. The flat surface of the transducer is placed against the scalp just behind and above the ear. Since air is completely reflective to ultrasound waves, a liquid or solid coupling material is needed for contact. Plain tap water has proven to be an excellent coupling medium. The transducer should be placed just below the hair line if possible since small amounts of air trapped around hairs may give rise to multiple confusing echoes. While observing the

* Ekoline 20—Smith-Kline Precision Co.

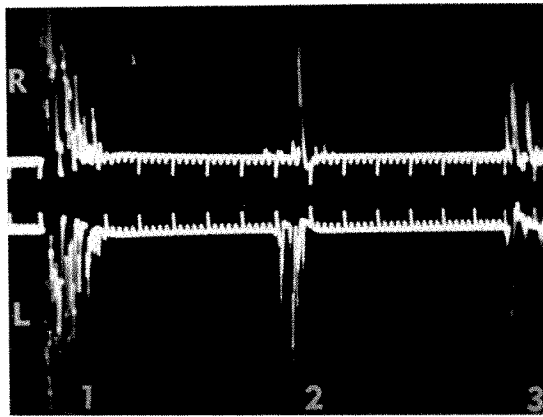


FIG. 1. Normal echoencephalogram. The salient features shown are the initial group of deflections or "main bang" from the crystal itself and the near side of the skull (1), the midline spike, which on the left to right trace presents as a double spike, probably from the walls of the third ventricle (2), and the far side echo, made up of echoes from the meninges, inner and outer skull tables and the air-skin interface (3).

oscilloscope screen, the transducer is gently rocked against the scalp until a strong midline echo spike and a satisfactory return from the far side of the skull are obtained. A picture is then made on the Polaroid camera, utilizing one half of the frame. The usual convention is to start on the right side utilizing the upper half of the frame, then from left to right using the bottom half. The transducer is then placed against the opposite side of the head and the lower half of the film used in a similar fashion. It is then possible to compare directly the echoes from both sides. This method is the A-Scan display.

The normal echoencephalogram (Fig. 1) shows (1) a "main bang" from the crystal and echoes from the near side of the skull, (2) a prominent midline echo and (3) returns from the far side of the skull. The far side echoes usually consist of several spikes, representing reflections from the meninges, inner and outer tables of the skull and the skin-air interface. It is extremely important that the "far-side" echoes are directly opposite when the two sides are compared. These may vary if asymmetry of the head

exists in which case corrective measurements can be made.

The midline echo is often a characteristic thin prominent spike. Frequently, with spreading of the tracing, two spikes may be obtained, presumably from the third ventricle walls. Good correlation has been obtained with two midline spikes in cases of proven dilatation of the third ventricle (Fig. 2). Because of this—the positioning of the transducer and the known difference in acoustic impedance between liquid and brain substance—we feel that the usual midline echo is probably arising from the posterior portion of the third ventricle. From several examinations done during pneumoencephalography, it has been shown that the usual position of the transducer during echoencephalography is over the posterior portion of the third ventricle and the upper part of the aqueduct of Sylvius (Fig. 3). Slight divergence of the beam could encompass the pineal gland and posterior septum pellucidum. There has been considerable controversy over the exact source of the midline echo and Jeppsson^{6,7} feels strongly that the pineal gland is the source of the midline echo. There has been no generally accepted source for the echo among workers in the field to date.

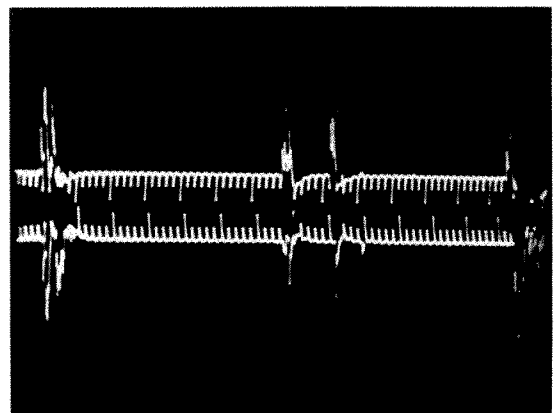


FIG. 2. Echoencephalogram in patient with almost complete occlusion of the fourth ventricle and generalized ventricular dilatation. The double spikes correspond exactly to the position of the walls of the third ventricle.

The range of variation from exact symmetry of the midline echoes when the sides are compared has been previously reported.¹⁰ It is generally agreed that a calculated midline displacement of more than 3 mm. in adults and 2 mm. in children should be considered abnormal and indicative of a significant shift. There are several methods of measurement if the skull is asymmetric. Variation in the method of presentation and recording, and magnification and slight degrees of rotation of roentgenograms, in addition to calcification in only a portion of the pineal gland, certainly make highly critical measurements of less than 1 mm. impractical and questionable for purposes of correlation. In cases where a midline echo is difficult to obtain or seems to vary in position, an averaging method using the "B-Scan" display can be used for verification.¹²

DISCUSSION

This method of echoencephalography has been used primarily as a supplement and complement to routine roentgenography of the skull. Its use for estimation of the midline structures of the skull has been evaluated in many large series besides this report.

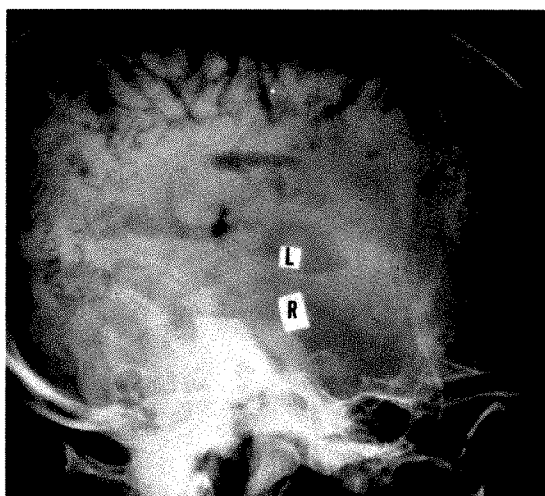


FIG. 3. Position of transducer during examination is noted by lead markers placed during pneumoencephalography. The position is over the inferior-posterior portion of the third ventricle.

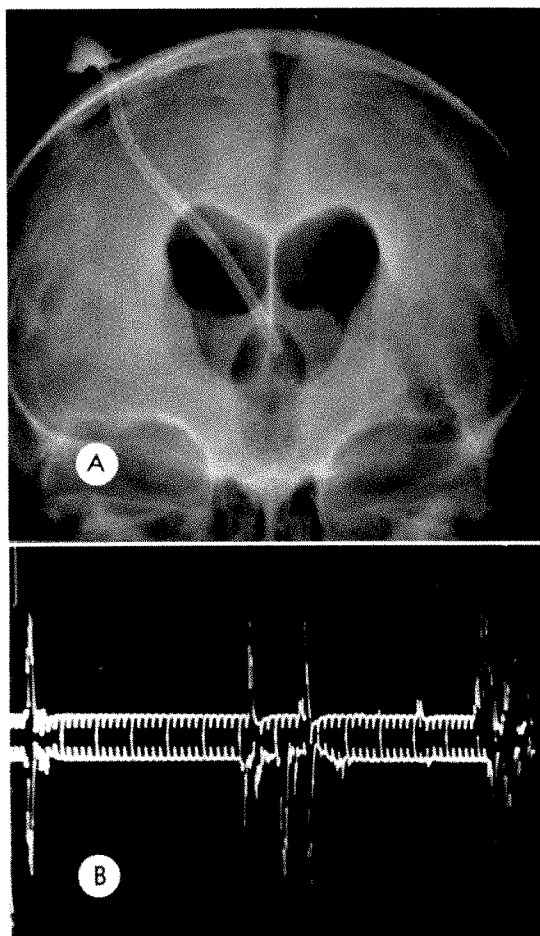


FIG. 4. (A) Ventriculogram shows generalized dilatation of the third and lateral ventricles in a patient with pinealoma. (B) Echoencephalogram shows a corresponding deflection caused by the walls of the wide third ventricle. On the left to right trace, a third midline spike can be seen. This may be arising from the septum pellucidum or the tumor itself.

In addition to the midline echo, there are other echoes obtained from examination of the skull which have proven to be of value. The presence of an enlarged third ventricle has been noted and proven in several cases of hydrocephalus, in a case of tuberculous meningitis with occlusion of the fourth ventricle and in a patient with pinealoma (Fig. 4, A and B). The twin spikes presumably representing the walls of the third ventricle have been obtained in many other cases and their position cor-

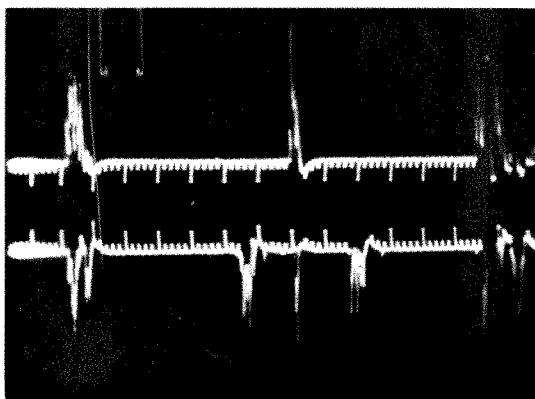


FIG. 5. The left to right trace shows characteristic deflections at a site corresponding to the usual position of the walls of the posterior portion of the body of the lateral ventricles, 1.5 cm. from the midline.

relates well with a previous roentgenographic study of the size of the third ventricle at different ages.³

Echoes have also been obtained from an area consistent with the position of the wall of the lateral ventricle in 66 cases (Fig. 5). The reflection would be in the region of the atrium of the lateral ventricle judging by its location and the position of the transducer on the skull. Multiple proven and unproven reflections have been noted between 1.4 and 2.2 cm. from the midline. This position would correlate with the posterior portion of the atrium of the lateral ventricle. Unfortunately, this does not explain why echoes are not obtained from the temporal horn, unless one can theorize that the absence of any large section of ventricular wall perpendicular to the beam does not allow a reflection from this area to be picked up by the transducer.

Tumor echoes have been reported by several other investigators. In our series there were 27 tumors. In only one of these cases was a persistent, constantly reproducible group of echoes obtained from the region of the tumor (Fig. 6, *A* and *B*). This lesion was proved to be a Grade IV glioblastoma multiforme, as were several other tumors in the group which did not present a characteristic echo. Two other cases showed similar echoes from the region of a known

tumor, but these findings were not constant.

Of interest in this group was the finding of a midline shift roentgenographically in only 14 of 27 cases. The nondisplacing tumors were mostly in the posterior fossa, but included two supratentorial invasive gliomas.

In 2 patients examined postoperatively, a large group of echoes was obtained from the site of surgery.

To date, 13 patients with subdural hematoma have been examined. In no case

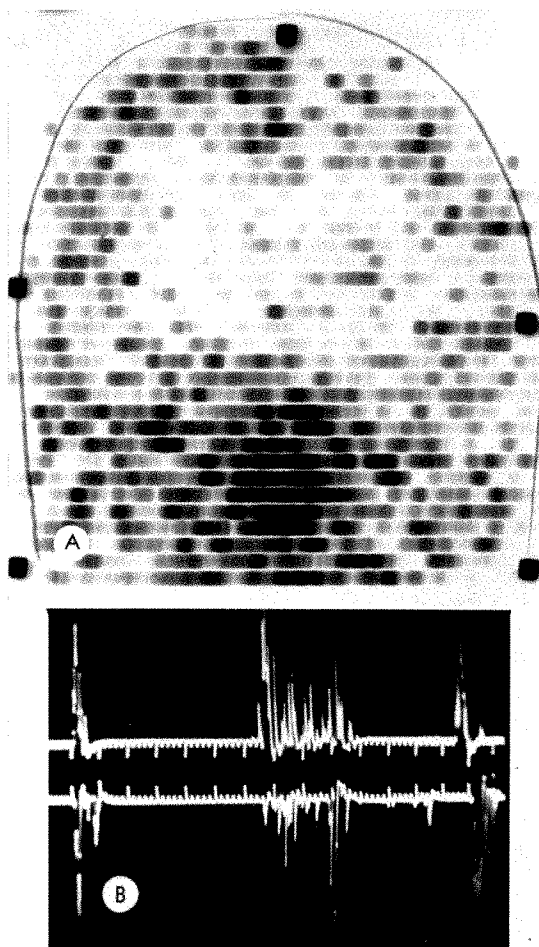


FIG. 6. (*A*) The isotope scan shows an area of increased activity deep in the left hemisphere, which was felt on arteriography to be a glioma. (*B*) Echoencephalogram showed a constant, completely reproducible group of echoes from the region of the tumor with a corresponding displacement of the midline structures.

was a reflection obtained from the interface between the pia mater and the subdural collection during routine examination in the acute phase (Fig. 7, *A*, *B* and *C*).

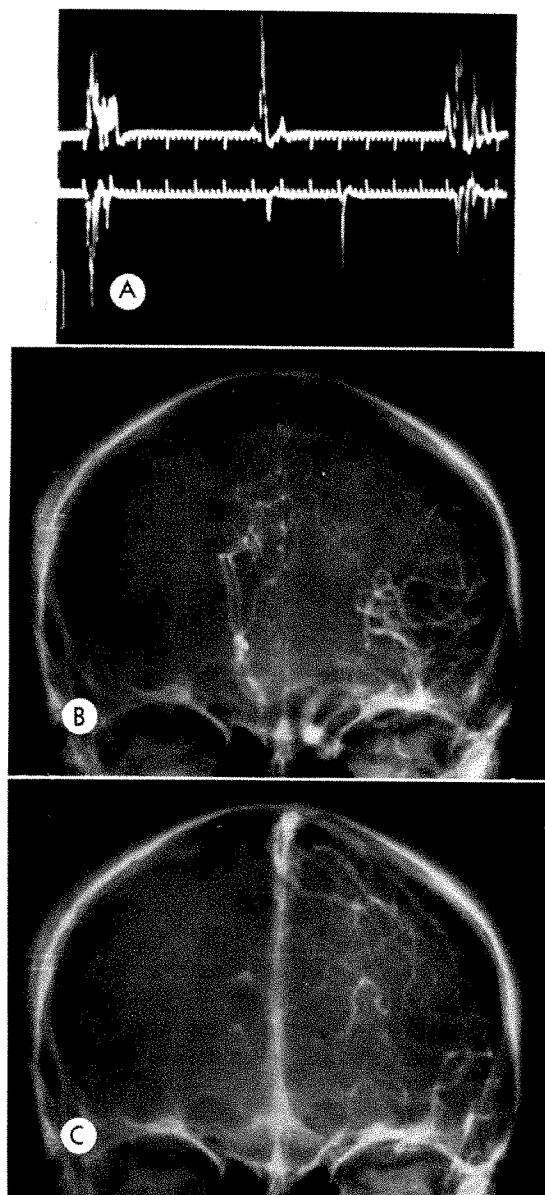


FIG. 7. (*A*) Echoencephalogram showing a marked midline displacement of 22 mm. toward the right side. (*B*) Arterial phase of the left carotid arteriogram showing a corresponding displacement of anterior and middle cerebral artery groups toward the right by a subdural collection. (*C*) Venous phase shows displacement of the internal cerebral vein and separation of cortical veins from the inner table of the skull by the proven subdural hematoma.

A prominent echo-spike was obtained from the interface of a chronic subdural hygroma in a 22 year old patient, whose history probably dated back at least 7 years.

One small but extremely interesting group of patients was encountered in this series. Four patients were examined whose routine roentgenography of the skull showed an apparent shift of pineal calcification. Routine roentgenography, incidentally, includes stereoscopic views in the posteroanterior, lateral and Chamberlain-Towne projections. One of these patients was referred to our neurosurgical department from another medical center for the further evaluation of this problem. In all of these cases, the echoencephalogram was normal with no evidence of midline shift. One patient, a female medical student, had suffered a minor head injury and was not studied further since her clinical condition was and is excellent. The other 3 patients were further examined by arteriography and pneumoencephalography with no evidence of a space taking lesion or other abnormality.

In retrospect, we feel that the calcification seen on the plain skull roentgenograms is probably within a lateral portion of a large pineal gland or in the free edge of the tentorium adjacent to the pineal and habenular region.

In our single case of bilateral subdural hematoma in this group, the midline was shifted due to a much larger collection on one side. However, with equal bilateral subdural hematomata no midline shift might be expected. This again indicates that this method is a supplement to the usual clinical and roentgenographic examinations.

In general hospital practice, one of the most valuable and helpful uses of echoencephalography has been in examining patients who are not able to be studied roentgenographically with any ease. This group includes postoperative neurosurgical patients, and particularly trauma cases. Two postoperative patients were found to have subdural hematomas after echoen-

cephalography demonstrated a shift of the midline structures.

Ninety-two patients in our series were examined because of trauma. The method lends itself to immediate usage in the accident dispensary or at the bedside. Many of this group were children where there is no possibility of pineal calcification. With a negative echoencephalogram following head trauma and an improving clinical situation, additional roentgenographic studies were almost never performed. This has added many unproven and repeated examinations on the same patient to our series but the examination has been of considerable value to the neurosurgeons in this situation.

Several patients in the group were examined at the bedside because of multiple severe injuries. Variations in the position of the midline could be followed on a daily basis and further roentgen studies were performed only if the patient's clinical condition and echoencephalographic findings indicated the necessity for possible neurosurgical intervention. Echoencephalography may prove to be of value in smaller institutions where immediate neuroradiologic and neurosurgical procedures are not readily available.

RESULTS

For the present report we have reviewed a series of 648 patients referred to the Department of Radiology for examination of the skull for varying reasons. All of the patients except 3 had, at least, a roentgenographic examination of the skull. Correlation of the results of echoencephalography was made with pineal calcification on plain roentgenograms of the skull, the position of vessels on arteriography and the position of the third ventricle on pneumoencephalography or ventriculography.

Seven hundred and twenty-three examinations were performed on the 648 patients. Of this number, the position of the midline was confirmed roentgenographically in 358, by correlation with one of the previously noted methods. Almost

all of the roentgenographically unconfirmed cases showed a clinical correlation with the echoencephalographic findings. Several cases showing abnormal echoencephalograms could not be confirmed because of the patient's poor general condition and the wish of the referring physician not to subject the patient to further study. Several others showed abnormal echo findings, but their good clinical condition has so far not warranted further roentgenographic study. The age of the patients ranged from newborn to 93 years and the sex distribution by age is shown in Table I. It can be seen that the younger age groups are predominantly male, primarily examined because of trauma.

The reasons for referral to the department for roentgen examination of the skull varied. Most of the patients presented with symptoms of intracranial disease. This group included 524 patients. Ninety-two patients were seen following head trauma. The remaining patients were examined for oto-rhinologic conditions or medical problems with possible related, but asymptomatic intracranial changes.

The examinations in 360 cases could not be correlated roentgenographically since no pineal calcification was present on the plain roentgenogram of the skull and their clinical condition did not indicate the need

TABLE I
AGE AND SEX DISTRIBUTION

	Male	Female
Age 0-9	33	11
10-19	32	25
20-29	53	37
30-39	44	37
40-49	47	52
50-59	61	55
60-69	51	36
70-79	31	31
80-89	4	7
90-99	1	0
	357	291
	Total 648	

Youngest—newborn; oldest—93 years.

TABLE II
ROENTGENOLOGICALLY VERIFIED CASES

1. No Midline Displacement	307 cases
Errors	5 cases
Accuracy	98%
2. Midline Displacement	51 cases
Errors	7 cases
Accuracy	87%

Over-all accuracy—96.6%.

for additional studies or, in a smaller number of cases, because of death.

The results of the roentgenologically verified cases are presented in Table II.

The accuracy in cases where no midline displacement was demonstrated was 98 per cent. Of the 5 errors in this group, 3 were due to the initial display of only one wall of a dilated third ventricle. These were later demonstrated to have a prominent double spike which did not manifest itself initially. These errors were all encountered early in our series and may be correctable with further experience.

Of the group with midline shift, only 87 per cent were correctly reported. Four of the 7 errors were in cases of subdural hematoma. It is possible that the location of the subdural hematoma was too high for the usual positioning of the transducer, but the position of the internal cerebral vein seen on the arteriogram in these cases suggests that the echoencephalogram should have shown a shift. It may be that reflections were obtained from the lower portion of an undisplaced third ventricle while the internal cerebral vein was displaced, but air studies were not performed.

The over-all accuracy of the method, over 96 per cent, suggests that the study is indeed worthwhile and warrants further use.

CONCLUSIONS

A large number of patients has been examined by echoencephalography under conditions of general hospital practice. The over-all accuracy of the method has been 96.6 per cent, suggesting that this method is a worthwhile supplement to the usual

procedures in the evaluation of intracranial problems. In addition to the usual midline position, other information about intracranial structures has been obtained and correlated with angiography, air studies and isotope scanning.

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ANATOMIC LOCALIZATION OF MIDLINE ECHO IN SONOGRAMS OF THE BRAIN*

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THE reluctance to accept sonography as a valid procedure in the evaluation of cerebral displacement persists in spite of almost a decade of extensive clinical application. This hesitancy appears unjustified inasmuch as verification of the results of the ultrasonic technique by angiography and pneumoencephalography exceeds 90 per cent.^{3,6,8} Conflicting reports as to the source of origin of the midline echo are in part responsible for this continuing skepticism. Studies have implicated many structures, prominent among which are the septum pellucidum,⁴ longitudinal cerebral fissure,¹⁰ third ventricle,^{1,3} and the pineal body.^{5,7} Thus, the acceptance of echoencephalograms remains limited since the clinician requires not only the knowledge of cerebral displacement, but also a reasonable estimate of the area undergoing shift. The present report attempts to establish a more specific anatomic source of the midline echo.

TECHNIQUE AND CLINICAL MATERIAL

The ultrasonic instrument* used for all determinations in this study employs a 2.25 megacycle, three-fourth inch round ceramic transducer with a half inch element. Calibrated records are obtained from an operating oscilloscope on Polaroid film. The method of examination is similar to that described by Smyth.⁹ This consists of paired readings taken from symmetrical points on opposite sides of the cranium ap-

proximately 1.5 to 2 cm. above and slightly posterior to the external auditory canal.

Ten patients were used in this study, ranging in age from 13 to 59 years with an average age of 37 years. Males and females were equally represented. In each, the echo was easily obtained and was midline. Patients with evidence of cerebral shift or increased intracranial pressure were excluded.

METHOD AND RESULTS

The assumption that a specific anatomic structure accounted for the typical midline echo was based on several observations made during routine examination. First, in order to produce the characteristic midline response, the transducer must be placed on a specific site in relation to the cranial vault, usually 1.5 to 2.0 cm. above and slightly behind the external auditory canal. Minor deviation of the transducer away from this position results in the loss of the characteristic midline response. This suggests that the structure responsible for the echo is relatively small. Second, in a few patients, the midline response cannot be obtained even though considerable effort is made to ensure optimum placement of the transducer. This raises the possibility that the midline source was not present; or if present, was of insufficient density to produce a detectable response. Third, the width of the midline echo, as determined in successive patients, is variable. This indicates that the structure producing the midline response has a finite lateral dimension which in some normal subjects exceeds several millimeters.

* Ekoline 20 Diagnostic Ultrasonoscope, manufactured by Smith-Kline Precision Co., 1500 Spring Garden Street, Philadelphia, Pennsylvania.

* Presented at the Sixty-fifth Annual Meeting of the American Roentgen Ray Society, Minneapolis, Minnesota, September 29-October 2, 1964.

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FIG. 1. Determination of ultrasonic trajectory with the arc-template.

To substantiate these speculations it is necessary to document the plane of the sound source as it traverses the cranial vault. This was accomplished by attaching the transducer to a rigid arc-template. The midline echo is located by moving both the transducer and the template (Fig. 1). Since sound travels in a straight line, the plane passing from the transducer to a point 180° from it defines the trajectory of the recorded sound beam. Metallic pins (electroencephalographic electrodes) are then applied to the scalp at the transducer site and to the site on the opposite side of the cranial

vault as defined by the arc-template. In each case studied, the sound beam was established from both sides of the cranial vault. Initially, two pins were used when scanning from right to left, and an additional two when scanning from the opposite direction. With experience, it was eventually possible to use only one set of pins representing the trajectory of sound from both directions.

Having thus established the plane and the midline location of the ultrasonic response, anatomic visualization was obtained by combining this technique with pneumoencephalography. In the 4 patients examined in this manner, a lumbar air study immediately followed pin placement. Figure 2*A* shows a case in which this combined technique was utilized. The pneumogram demonstrated atrophy of the caudate nuclei compatible with the clinical diagnosis of Huntington's chorea. The pins which are posteriorly directed represent sound scanning from right to left; those anteriorly directed define the left to right trajectory. In the study shown, the two posteriorly placed pins overlap and their trajectory passes through the area of the pineal body. Rotation of the head so that

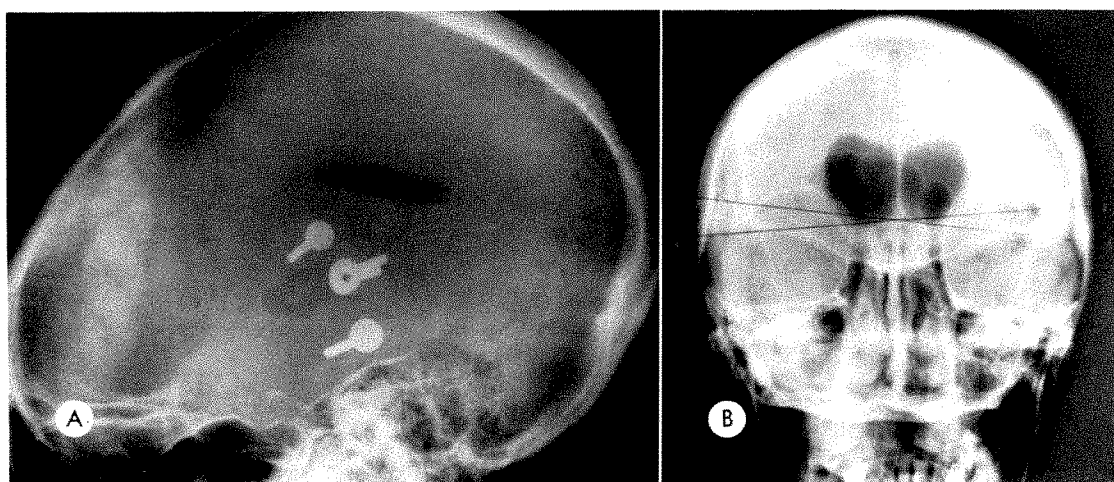


FIG. 2. (*A*) Documentation of sound trajectory from both sides of cranial vault after pin placement with arc-template. Superimposed pins define the sound plane from right to left and cover pineal area as demonstrated on the pneumogram. Anteriorly directed pins, although not superimposed in this illustration also cover pineal area. (*B*) Diagonal lines illustrate sound trajectory through the cranial vault as viewed from an anterior plane. In this projection these lines intersect at the point of origin of the echoencephalographic response.

the anterior pins are superimposed produces a similar result. Figure 2*B* is an anteroposterior projection of the same patient. The diagonal lines extend from the pins described on the previous roentgenogram (Fig. 2*A*) and define sound trajectory through the cranial vault as viewed from an anterior plane. In this projection, these lines intersect at the point of origin of the echoencephalographic response.

Observations on the 4 patients studied are presented in Figure 3. Each symbol represents the trajectory of the sound source as it passes through midline structures. The pineal area was implicated in 3 of the 4 cases. In the fourth subject the point of origin of the midline echo appeared to be a prominent supra-pineal recess. Roentgenographic calcification of the pineal was present in only 1 of these cases.

Localization to the pineal area prompted a modification of approach in that the arc-template technique was next performed on 6 patients with roentgenographically calcified pineal bodies. This simplification elimi-



FIG. 3. Composite illustration indicating source of the midline echo in 4 patients studied with arc-template and pneumography. The symbols represent trajectory of sound beam through midline structures. The pineal gland was implicated in 3 of the 4 patients.

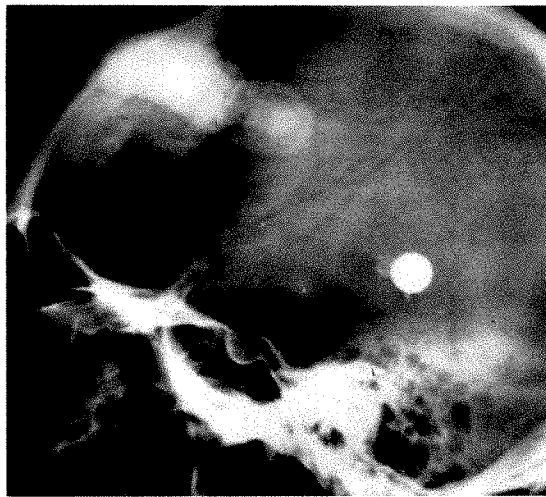


FIG. 4. Superimposed pins define sound trajectory from both sides of cranial vault. This plane passes through the rostral half of the calcified pineal gland.

nated the use of air although in the previous series the stereotactic method always preceded pneumoencephalography. Figure 4 shows the result obtained in a 41 year old female with rheumatic valvular disease. In this case the superimposed pins define the sound trajectory from both directions and pass through the superior aspect of the pineal calcification.

The combined results of this series are illustrated in Figure 5. The triangular sym-



FIG. 5. Symbols define the trajectory of the sound beam as it was related to pineal calcification in the 6 patients studied.

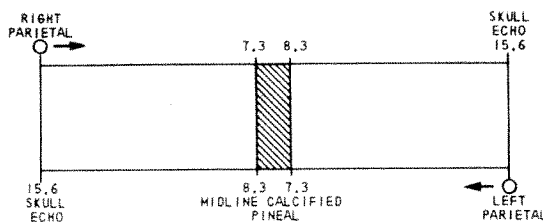
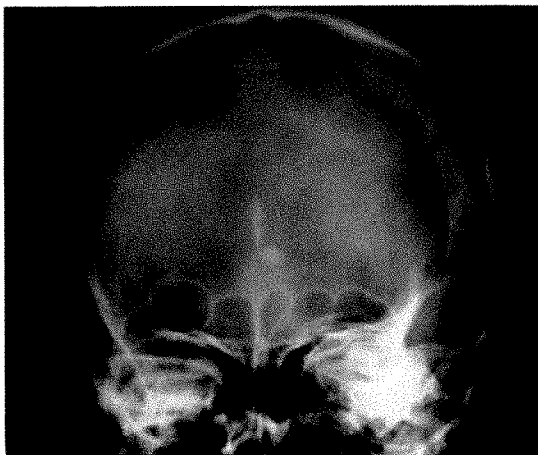


FIG. 6. Diagram illustrates the echo obtained from a patient with a large calcified pineal gland. The ultrasonic response of 10 mm. is within 1 mm. of the roentgenographic pineal measurement.

bols define the trajectory of the sound beam. The localization of the source of the midline echo by this technique corresponds to the position of the calcified pineal body in each of the 6 studies.

The patients in Figure 6 and 7 are presented because they provide roentgenographic visualization of unusually large calcified pineal bodies and demonstrate another characteristic of the midline echo. As in the previous studies, the pineal gland was documented by the arc-template to be the source of the midline response. In each, it was also possible to determine the width of the ultrasonic response and to compare it to the width of the roentgenographically calcified pineal gland. In the first patient (Fig. 6) the ultrasonic width of 10 mm. was within 1 mm. of its roentgenographic counterpart after the latter was corrected for image amplification. The width of the roentgenographically calcified pineal gland in the second case (Fig. 7) was demon-

strated with comparable accuracy by ultrasound. In addition, it was also possible to delineate the central radiolucency by sonography.

DISCUSSION

Opinions as to the anatomic origin of the midline echo are as numerous as the techniques used in its determination. The efficacy of any approach depends on its ability to define the anatomic source of the midline echo without altering the physical characteristics of the intracranial contents. Studies on cadavers probably do not fulfill this requirement. The acoustical impedance of postmortem material may vary considerably from that of its viable counterpart. Echoencephalographic records attempting to reproduce the midline echo, using identical trajectory, are altered after death. Extraneous spikes, nonexistent during life, make their appearance. These can be of such number and amplitude as to obscure or distort the midline echo. Attempts to obliterate the midline echo by removal or

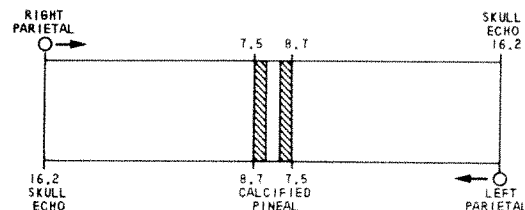


FIG. 7. Diagram illustrates quantitative documentation of ring-like pineal calcification by ultrasound.

modification of specific anatomic structures are limited by artifact produced during manipulation of cerebral tissue. Techniques which alter acoustical impedance during life are also subject to criticism. Methods utilizing pneumoencephalography to document the source of the normal midline response are potentially unreliable because of the introduction of air into spaces previously filled with cerebral spinal fluid. Under these circumstances, delineation of the third ventricle as well as the cisterns is to be expected. That these structures account for the midline response of the routine echoencephalogram must be accepted with reservation. In the present study, this objection is obviated by utilizing the arc-template to determine the midline echo prior to the introduction of air.

It is possible that calcification of the pineal body may account for its effectiveness as a source of the midline echo. Adequate echoencephalographic results, however, do not depend on roentgenographic visualization. In this study, it was possible to confirm the pineal localization with or without demonstrable calcification.

SUMMARY

The results of this study confirm the clinical impression of a specific circumscribed anatomic source of the midline echo. The trajectory of the ultrasonic beam passed consistently through the pineal body in all but 1 of 10 subjects considered. In the 1 subject the sound beam passed through a prominent suprapineal recess. Further substantiation of the pineal origin was provided by the ability to correlate roentgenographic and sonographic width of the pineal gland. The conclusion that the source of the echo corresponds to the position of the pineal body confirms previous reports that the sonogram may fail to demonstrate displacement in association with lesions producing predominantly anterior cerebral shift.^{2,7,8} These observations do not necessarily exclude the possibility of other ana-

tomic areas. They do, however, suggest that the information provided by the routine echoencephalogram parallels that which can be derived from the roentgenographic localization of the pineal body.

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POSITIVE BRAIN SCAN IN NON-SPACE-OCCUPYING LESIONS*

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RECENT advances in neuroradiographic methodology have included radioisotopic brain scanning. In this procedure, it is presumed that a cerebral lesion will be detected if it disrupts the blood-brain barrier. With the use of more sensitive instruments, more specific radioisotopic preparations and improved technique, this study has become a reliable indicator of cerebral neoplasms and other space-occupying lesions such as arteriovenous malformations, brain abscess, cerebral granuloma, and others.

Also, there have been scattered reports of the occasional findings of localized increases of tracer uptake by encephalomalacic lesions due to vascular occlusive disease. With one exception—these have all been in the acute phase. The problem of differentiating these positive scans from those due to mass lesions immediately comes to mind. However, little data have been reported on sequential scans in individual stroke patients.

We have recently had the opportunity to follow several patients whose clinical course and angiographic findings were quite typical of encephalomalacic rather than neoplastic processes. All of these patients had definite localized areas of increased uptake of Hg^{203} radioisotope. These areas corresponded well with the clinical localization. These "positive" scans were obtained in the first few weeks of the illness. Repeat scans were normal 4 weeks or later. Two representative cases are reported here.

METHOD

The patient is first given an intramuscular injection of 1 cc. mercurhydrin at ap-

proximately 5:00 P.M. the evening before the Hg^{203} neohydrin is to be injected. Ten microcuries of Hg^{203} neohydrin per kilogram body weight is injected intravenously. Two and a half to three and a half hours after the Hg^{203} neohydrin injection (except when vascular anomalies are suspected), the patient is scanned with the Picker Magnascanner.

Because of the low count rate, a low "count per minute range differential" is used. The count rate is determined with the 19 hole collimator over the area of highest radioactivity in the patient's skull (excluding sinuses). The "high voltage" is adjusted to 1,000 volts (density of 1.8 on the photoscan). The collimator is moved away from the patient. The voltage should drop below 700 volts, usually from 300 to 500 volts (density of 0.3 on the photoscan). The scanning speed is set at 36 cm. per minute and a spacing of 0.35 cm. is used with the small photoaperture. Speed is now constant, so density and dot factors are a function of count rate. The discrimination circuit is set to 210–330 kev. Both photo and dot scans are made simultaneously. The views of the scan are selected according to the clinical findings. At least two views are obtained—either posteroanterior or anteroposterior, and either right and/or left lateral. Oblique views are added when indicated.

REPORT OF CASES

CASE 1. J. McD. was a 52 year old man who had had several episodes of transient hemiparesis since 1960. One of these episodes resulted in 10 days of hemiparesis and dysphasia in 1961. Complete recovery ensued. He was admitted to the Presbyterian-Univers-

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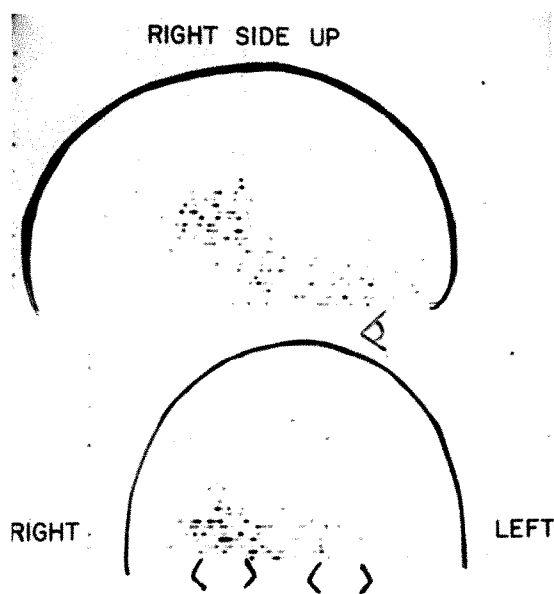


FIG. 1. Case 1. The initial Hg^{203} neohydrin brain scan on October 24, 1963 revealed a definite area of abnormally increased radioactivity uptake. This was at the acute stage of the patient's disease.

sity Hospital in October, 1963, because of the sudden onset of complete left hemiplegia.

An examination revealed a flaccid left hemiplegia and lower left facial paralysis. The patient was mildly confused and obtunded and manifested both depression and a moderate

organic mental syndrome. There were several stigmata of cortical sensory loss on the left side.

Cerebrospinal fluid was normal except for a protein of 72 mg. per cent. The skull roentgenograms were normal and failed to reveal any calcification of the pineal gland. The electroencephalogram was abnormal but no clear-cut focus could be localized. A radioisotopic brain scan was made with Hg^{203} neohydrin on the third day of the illness. This revealed a definite area of increased uptake in the right parietal region (Fig. 1). Because of the lack of clinical improvement and the marked organic mental syndrome, right carotid angiography was performed 8 days after admission. This was entirely within normal limits.

In the second week of the patient's illness, the brain scan was repeated and was again found to be "positive." In the fourth week, at a time when the patient had still failed to improve, a third scan was almost normal (Fig. 2). Over the ensuing 4 months, he gradually improved. When last seen in February, 1964, he had only a moderate left hemiparesis and hemisensory deficit but was markedly demented.

CASE II. E.H. was a 60 year old man who was well until 3 months prior to admission. At the time, his wife began to note frequent episodic confusion, forgetfulness, and a blunting of

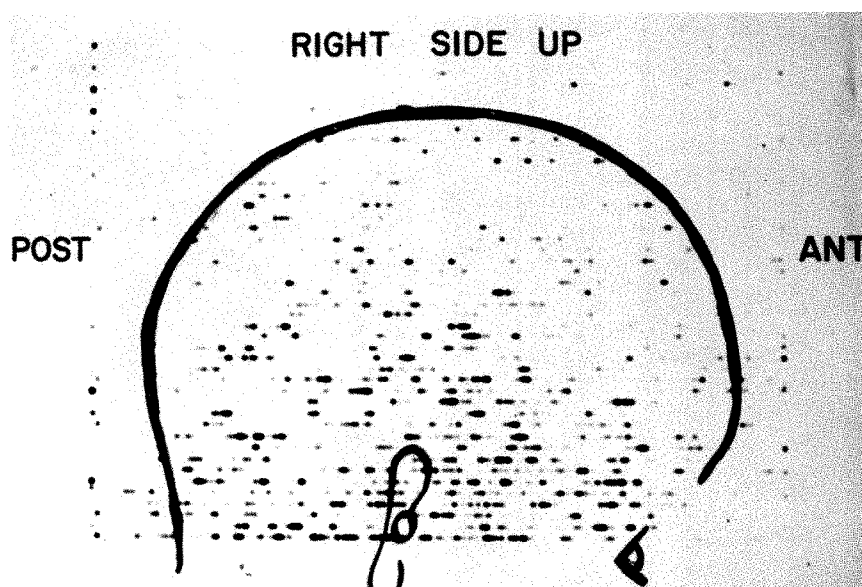


FIG. 2. Case 1. The repeat Hg^{203} neohydrin brain scan on November 27, 1963 revealed almost complete disappearance of the area of increased radioactivity uptake.

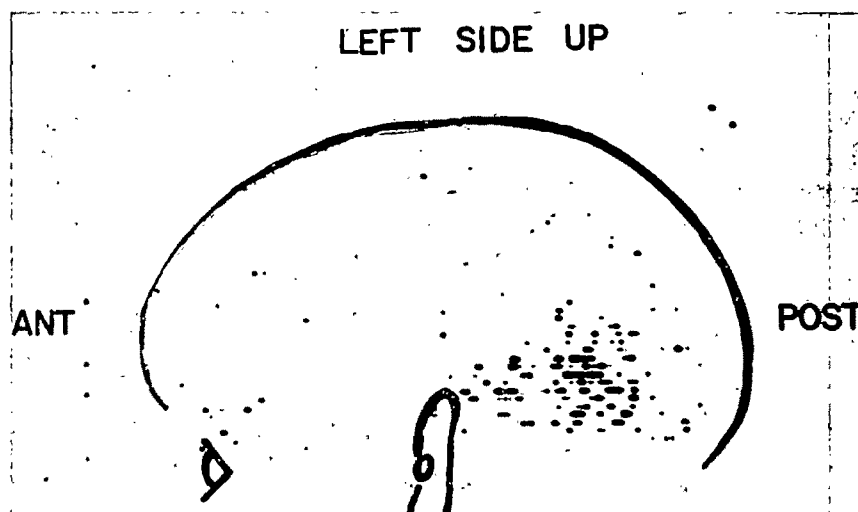


FIG. 3. Case II. The initial Hg^{203} neohydrin brain scan on October 28, 1963 showed a definite area of abnormally increased radioactivity uptake.

affect. Two months later, he began to note left sided headaches of increasing severity and frequency. One week prior to admission, he was hospitalized elsewhere because of an acute brain syndrome over a period of 36 hours. This consisted of marked central (syntactical) dysphasia, confusion, and constant left sided head pain. No motor phenomena were observed. Routine studies, skull roentgenograms and cerebrospinal fluid were normal. A brain scan was made on the second hospital day using radioiodinated serum albumin.* This showed a definite area of increased uptake in the left parietal region.

The patient was transferred to the Presbyterian-University Hospital on the eighth day of the acute illness. Examination revealed a marked central dysphasia, marked dysnomia, left-right confusion, dyschiria, and a right sensory extinction. There was absence of hemiparesis, hyperreflexia, and confusion. The headaches had ceased.

A repeat brain scan on the eighth day with Hg^{203} neohydrin again revealed the increased area of uptake in the left parietal lobe (Fig. 3). Despite a definite improvement over the next few days, it was thought necessary to exclude a malignant glioma. Left carotid angiography was performed on the fifteenth hospital day. This failed to reveal a mass lesion or "tumor"

vessel. Over the next 3 weeks, the patient improved to near normality. The last examination revealed only minimal dysnomic dysphasia. A third brain scan with Hg^{203} neohydrin was made in the fifth week and was normal (Fig. 4).

DISCUSSION

The first case demonstrated the typical course and clinical findings of encephalomalacia of the right parietal region due to occlusive cerebrovascular disease, while the second had a progressive left parietal lobe syndrome with the problem of differentiating between a rapidly expanding tumor and

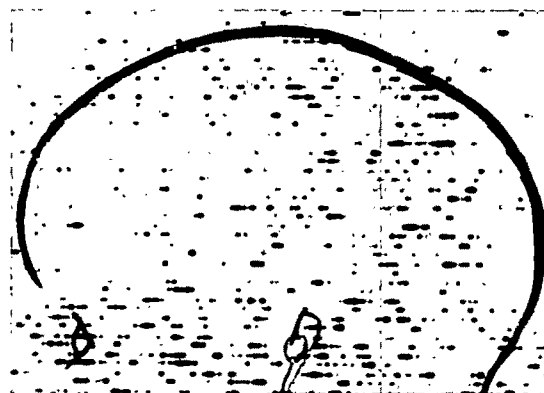


FIG. 4. Case II. The repeat Hg^{203} brain scan on November 27, 1963 revealed complete disappearance of the area of increased radioactivity uptake.

* Medical and radioisotopic services of Dr. David Chamovitz, Aliquippa General Hospital, Aliquippa, Pa.

progressive ischemia and infarction of a vascular basis. The angiograms clearly eliminated tumor in both cases.

In McAfee and Taxdal's⁴ excellent series, patients with encephalomalacia of less than 2 weeks' duration had "positive" RISA scans. They cite many examples of old malacia of several months' duration with normal scans. One case of an old malacia with a "positive scan" was subjected to an unproductive craniotomy. Dugger and Pepper's² series contains 3 cases of increased radioisotopic uptake with malacic lesions, 2 proven by angiography. However, the duration of the lesions is not mentioned. In 1 case, a repeat scan 4 weeks later was normal.

In the past 2 years, over 100 brain scans have been made on Neurology Service patients with chronic encephalomalacic lesions at the Presbyterian-University Hospital and the Veterans Administration Hospital. These patients had all had "strokes" 2 or more months before the scans were performed and they were all reported as normal. In addition to the 2 cases described in this paper, an acute case has been recently evaluated by the Veterans Administration Hospital Radioisotope Service.* This case was clinically typical of acute occlusive vascular disease, but angiographic confirmation was not deemed necessary. This man had a "positive" brain scan (RISA) in the first week of his illness and a "negative" scan at 5 weeks. Two other similar cases were observed. Many series in the literature contain examples of "old strokes" with normal scans.

Thus, it is seen that lesions other than space-occupying neoplasms may alter the blood-brain barrier sufficiently to cause a localized area of increased uptake of various radioisotopic tracer materials. Among these is acute encephalomalacia due to occlusive cerebrovascular disease. Although the number of cases reported and referred to here is small, the almost invariable ab-

sence of "positive" scans in large numbers of cases of more than 8 weeks' duration would seem to justify certain tentative conclusions. Of course, it seems obvious that a "positive" brain scan which does not correlate well with the clinical and other neurodiagnostic studies should be viewed with caution. In this situation, if circumstances permit, repeat scanning in 4 to 6 weeks may be very useful and revealing.

SUMMARY AND CONCLUSIONS

Case histories are presented of 2 patients in whom the clinical course and the angiographic findings were quite typical of encephalomalacia. Both of these patients had definite areas of increased uptake of Hg²⁰³ neohydrin. These areas correlated well with the clinical features. Three other similar cases were also observed.

The "positive" scans were obtained in the first week of the illnesses. Repeat scans in the second week were again positive, but in both cases, scans were normal at 4 weeks.

These 2 instances and the many normal scans in patients with older malacic lesions suggest that acute encephalomalacia is not distinguishable from cerebral neoplasm by brain scanning. However, persistence of the localized area of uptake for longer than 4 to 6 weeks is indicative of a cerebral neoplasm or some other lesion rather than encephalomalacia. The fact that other than space-occupying tumors may be detected by this method is re-emphasized.

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The technical help of Mr. Ronald T. Fabian with the brain scans is gratefully acknowledged.

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* Dr. John Vester, Chief of Service at Veterans Administration Hospital, Pittsburgh, Pa.

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AIRWAY DYNAMICS IN BRONCHIECTASIS*

A COMBINED CINEFLUOROGRAPHIC-MANOMETRIC STUDY

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THE application of combined cinefluorographic and manometric techniques to the study of the bronchial tree in recent years has revealed a significant difference in the dynamic activity of the bronchi in normal subjects and in patients with certain obstructive lung diseases.³ Measurements of the caliber of several divisions of the bronchial tree in full inspiration and in forced expiration or cough have shown a disproportionate collapse of the lower-lobe bronchi on forced expiration in patients with chronic bronchitis or emphysema, in contrast to a uniform reduction in caliber of all bronchial divisions in normal subjects.¹ The recording of intrabronchial pressures, pleural pressure and air flow at the mouth simultaneously with cinebronchography has revealed a large pressure drop across the collapsing bronchus on forced expiration in patients with chronic bronchitis and emphysema, compared with a gradual decrease in pressure along the length of the bronchial tree in normal subjects, indicating that the large airways, particularly the lobar bronchi, exert a significant effect in producing restriction of air flow on forced expiration in these obstructive airway diseases.³ Although the exact mechanism whereby this selective collapse occurs is not yet known, it has been reasonably assumed to be related, at least in part, to an intrinsic abnormality of the bronchial wall itself, possibly in the form of a softening which could conceivably induce abnormal flaccidity.

In view of these observations on patients with chronic bronchitis and emphysema, it

appeared reasonable to suspect that other diseases characterized by bronchial damage might show similar dynamic abnormalities. Our attention was thus directed towards bronchiectasis, the study of which it was felt might be productive of information that could supply further clues as to the nature of this phenomenon.

DEFINITION OF BRONCHIECTASIS

The traditional definition of bronchiectasis as the irreversible dilatation of one or more segmental bronchi is no longer adequate to separate the cylindrical or fusiform variety of this disease from chronic bronchitis, the pathogenesis and clinical effects of which are different. A loss of normal bronchial tapering is not an uncommon bronchographic finding in chronic bronchitis,^{5,7,8} so that dilatation of a bronchus *in itself* cannot serve as a distinguishing feature. Since chronic bronchitis tends to be a generalized disease of the bronchial tree and cylindrical bronchiectasis localized, we prefer to regard *anatomical distribution* of bronchial dilatation as the main criterion for differentiation, and to restrict the diagnosis of cylindrical bronchiectasis to that state in which bronchial involvement is localized to one or more segments, in the presence of normal bronchi elsewhere in the same lobe or lung.

CASE MATERIAL

The cinebronchograms of all patients with bronchiectasis examined by the cinefluorographic technique since 1959 were reviewed, and those in which the detail

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‡ Jonathan Meakins Memorial Fellow of McGill University. From the Joint Cardio-Respiratory Service, Department of Medicine, Royal Victoria Hospital.

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and contrast were of adequate quality to allow accurate measurement of bronchial calibers were selected. On this basis, 20 cinebronchograms of 17 patients (3 had bilateral studies) became the subject matter of the investigation. Combined cine-fluorographic-manometric studies in which bronchial calibers, intrabronchial and pleural pressures and air flow at the mouth were recorded simultaneously were performed in 4 instances (3 patients).

Since some selection was used, the ratio of types of bronchiectasis in this series does not necessarily represent a true index of relative frequency.

METHODS

The technique of examination, methods of measurement and possible sources of error have been described in detail elsewhere.¹ Briefly, the equipment consists of a 16-mm. camera with synchronized exposures recording from the output phosphor of a Picker 8-inch or 9-inch image amplifier: the former employs a mirror system and the latter an image orthicon television system for fluoroscopic monitoring. Du Pont Cineray film was used exclusively, largely because of its fine grain and excellent detail. Dosage rates with both pieces of apparatus are within a reasonable range, amounting to 8 r per minute or less at the skin surface with the frame speeds commonly used. Because of the rapidity with which bronchi close during forced expiration or cough, of the order of 30 milliseconds or less, it was necessary to use frame speeds of 15 or, preferably, 30 per second to prevent blurring of images.

After instillation of opaque medium, the patient was placed in the upright position and rotated under fluoroscopic control until maximal separation of bronchi was obtained, generally at about 30° from the frontal plane. Tracheal and bronchial movements were then recorded during quiet respiration, during maximal inspiration and forced expiration, and finally during violent coughing.

Measurements of bronchial diameters

were made from single frames of the cine-film projected from a standard analyzer-type projector that reflected the image off a mirror on to a frosted-glass plate. Projection distances were not critical since the factor of image magnification could be corrected through the presence of a radiopaque tip on the bronchial catheter; since the catheter tip was endobronchial in position and its precise length was known, true bronchial diameters could be deduced from the magnified measurements with only insignificant potential error.

In all cases, measurements were made of the following bronchial segments:

1. The bronchus to the lower lobe, at a point within 5 mm. distal to the origin of its superior or apical segmental bronchus.
2. One or more of the bronchiectatic segments within 5 mm. of their origin at bifurcation.
3. One or more of the bronchiectatic segments at a point of their greatest dilatation.

The maximal diameter in full inspiration and the minimal diameter in forced expiration or cough were measured at each site. There was little difference generally between the minimal caliber reached on a single forced expiration and on a cough, although it was more difficult to teach patients to carry out the former procedure well. Additional measurements of the main-stem bronchi and of the right intermediate-stem bronchus were made in many cases, but these were consistently within normal limits and, therefore, were not included in the final data.

In 4 instances (3 patients), using a technique described previously,² measurements were made simultaneously during cine-fluorography, of intrabronchial pressure in a bronchiectatic segment and at other levels in the tracheobronchial tree, and of esophageal pressure and flow at the mouth. Briefly, bronchial pressures were measured through an air-filled side-hole vinyl catheter that was kept patent by a constant flush of air from a compressed-air tank connected by a needle valve. Esophageal pres-

TABLE I
ANALYSIS OF 20 CINEBRONCHOGRAPHIC STUDIES PERFORMED ON 17 PATIENTS

	1	2	3	4	5	6	7	8	9	10	11	12
	Case No.	Age	Sex	Type of Bronchiectasis	Side Involved	No. of Segments Involved	Lower-lobe Bronchus		Segmental Origins*		Bronchiectatic Segments*	
							Diameter Insp./Exp. (mm.)	Reduction in Caliber (%)	Diameter Insp./Exp. (mm.)	Reduction in Caliber (%)	Diameter Insp./Exp. (mm.)	Reduction in Caliber (%)
Group A	1	31	M	Cylindrical	L	3	10.7/5.4	50	6.2/5.0	19	5.6/3.8	32
	2	34	F	Cylindrical	L	6	10.0/6.1	39	7.1/4.6	34	6.9/4.6	33
	3	23	F	Cylindrical	L	3	10.7/6.6	38	6.7/5.4	20	8.3/5.3	36
	14	23	M	Cylindrical	L	2	10.0/5.6	44	5.6/3.1	45	5.6/3.7	34
	20	16	F	Cystic	L	4	10.7/7.0	35	8.0/4.0	50	15.0/7.0	53
Group B	4	38	M	Varicose	R same patient	5	9.6/4.8	50	8.0/3.2	60	8.4/7.0	17
	5	38	M	Varicose	L	6	10.4/4.8	54	6.5/1.6	75	9.9/7.3	26
	8	25	F	Varicose	L	3	9.7/2.4	75	8.4/2.8	67	12.9/10.8	16
	11	61	M	Varicose	R	3	12.0/6.0	50	9.0/3.0	67	9.0/7.0	22
	12	35	M	Varicose	R same patient	4	9.6/2.4	75	8.0/2.4	70	7.6/6.9	9
	13	35	M	Varicose	L	5	10.0/3.0	70	8.0/3.0	63	8.0/6.0	25
	18	30	F	Varicose	R same patient	7	12.0/7.6	37	7.6/2.5	67	8.0/6.3	20
	19	30	F	Varicose	L	5	12.0/2.5	79	7.6/6.0	11	8.4/8.4	0
	19	30	F	Varicose	L	5	12.0/2.5	79	7.6/6.0	11	8.4/8.4	0
Group C	6	29	F	Cystic	R	7	8.8/2.2	75	5.8/2.5	56	21.5/19.5	9
	7	54	F	Cystic	R	2	9.6/5.6	42	6.4/2.4	63	11.2/11.2	0
	9	42	F	Cystic	L	6	11.5/3.0	74	8.4/4.0	52	15.3/15.3	0
	10	77	M	Cystic	L	6	12.0/2.4	80	†		16.3/16.3	0
	15	26	F	Cystic	R	3	6.4/1.6	75	5.6/1.6	71	9.7/9.7	0
	16	47	F	Cystic	L	6	6.6/2.2	66	4.5/1.7	62	15.0/12.0	20
	17	21	F	Cystic	L	1	6.4/3.2	50	4.8/1.6	66	11.0/11.0	0

* In most cases, figures represent an average of several measured segments.

† Measurements could not be obtained for technical reasons.

sure, which was used as an index of pleural pressure, was measured with an esophageal balloon and catheter. Bronchial and esophageal pressures were related to mouth pressure, using suitable differential pressure transducers.* Flow at the mouth was measured either by pneumotachygraph† or by differentiating spirometer.‡ Each exposure of the cinefluorographic circuit generated an electrical signal that was recorded on a multichannel recorder§ together with the two pressures and flow. Subsequently, a frame-by-frame measurement of airway diameter permitted assessment of bronchial caliber, the pressure inside it, pleural pressure and flow at the mouth. From the esophageal or pleural pressure tracing, alveolar pressure was estimated by subtracting

from the pleural pressure that caused by elastic recoil.

RESULTS

CINEFLUOROGRAPHY

In Table I are listed the inspiratory and expiratory bronchial measurements obtained (columns 7, 9 and 11), the age and sex of the patient, the side involved and the number of bronchiectatic segments. Columns 8, 10 and 12 show the percentage reduction in caliber of each bronchial segment from the maximal inspiratory to the minimal expiratory diameter, and it is to these figures that attention is specifically directed.

When the figures for percentage reduction in caliber were reviewed originally, it became apparent that the 20 bronchograms could be conveniently divided into two distinct groups—one in which bronchial dynamics were essentially normal (5 broncho-

* Sanborn 267B transducers.

† NIH large flow-meter with Stratham P.97-D strain-gauge.

‡ Med-Science Electronics wedge spirometer.

§ Four-channel Sanborn Polyviso.

grams), and a second, much larger, group of 15 bronchograms in which dynamics were disturbed in a manner uniform in pattern although differing in degree.

In the first group, reduction in caliber of the main bronchi to the lower lobe and of the bronchial origins was 50 per cent or less and of the bronchiectatic spaces was 30 per cent or greater. The *average* expiratory reduction of the bronchiectatic segments (41 per cent) compared favorably with that of 45 per cent found in the same segments in 7 normal subjects.¹ Average diameters on maximal inspiration in both the patients (Table II) and the normal subjects were similar except that, in the former, the dilatation and loss of tapering of the bronchiectatic segments themselves were reflected in an average caliber more than twice the normal (8.3 mm. compared with 3.6 mm.). Thus, it was apparent that, in these 5 patients, the bronchial response to forced expiration was roughly proportional down the whole length of the bronchial tree, despite the presence of extensive disease in the peripheral divisions (Fig. 1, *A* and *B*).

By contrast, the second, considerably larger, group of 15 bronchograms (12 patients) showed a striking departure from the normal pattern (Fig. 2 through 4, inclusive). With one exception (Case 18, Table

1), the lower-lobe bronchus showed a reduction in caliber of 50 per cent or more, and although this figure was common to certain patients in both groups, the average reduction was significantly higher in the second group (60 per cent) than in the first (42 per cent). However, the factor that clearly segregated the two groups was the reaction of the bronchiectatic segments, both at their origins and at their points of maximal dilatation. As with the lower-lobe bronchi, the origins of the bronchiectatic segments showed a remarkable tendency to collapse on forced expiration or cough, the smallest reduction in caliber being 52 per cent and the average 60 per cent (Fig. 3, *C* and *D*). In contrast, these same segments at their points of maximal dilatation showed an exactly opposite response to cough; although the range was greater (0 to 26 per cent), the average reduction in caliber in the second group was only 11 per cent compared with 41 per cent in the first group and 45 per cent in the normal subjects.

Thus, the difference between the two groups of patients was not so much in a dissimilarity in response of *the same* bronchial divisions as in the combination of reactions of *all three* segments in any one bronchial tree. In the first group, the response to forced expiration was roughly

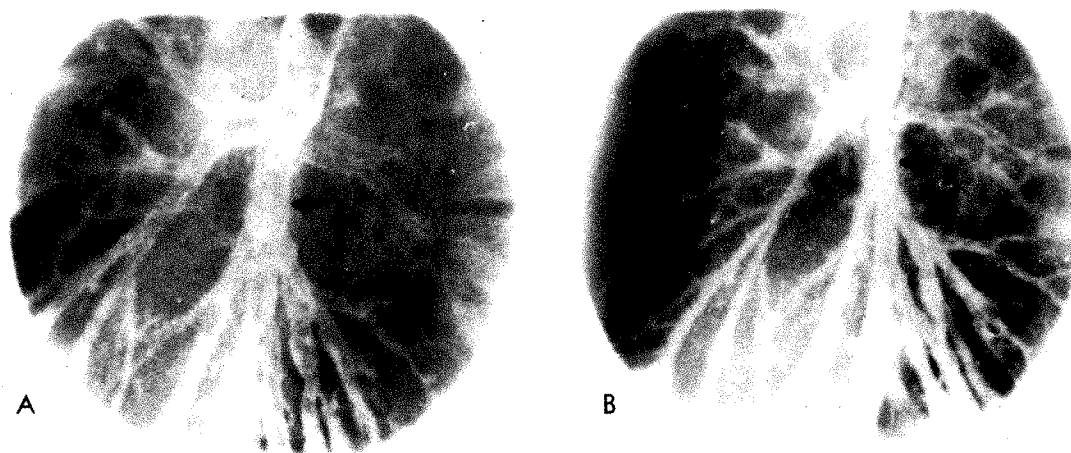


FIG. 1. Case 1. *Cylindrical bronchiectasis*. Representative cinefluorographic frames showing the maximal diameter on full inspiration (*A*) and the minimal diameter on coughing (*B*). Both the main lower-lobe bronchus (arrows) and the bronchiectatic segments show a normal and proportionate reduction in caliber on coughing, amounting to 50 per cent and 32 per cent, respectively, of their inspiratory caliber.

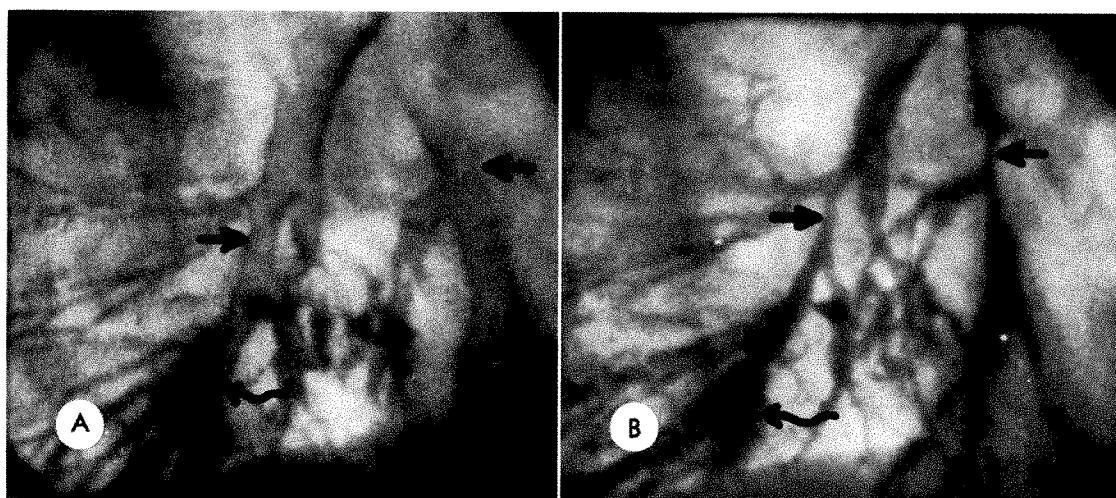


FIG. 2. Case 12 and 13. *Varicose bronchiectasis*. Representative cinefluorographic frames showing the maximal diameter on full inspiration (A) and the minimal diameter on coughing (B). Portions of both bronchial trees are included in the field. The main bronchi to both lower lobes (straight arrows) show a collapse of their lumina on cough, amounting to 75 per cent on the right and 70 per cent on the left, while the bronchiectatic segments, particularly on the right (curved arrows), have undergone little change in caliber (see Table 1). Note that the contrast medium has moved proximally on cough but has not been expelled.

equal and proportionate down the length of the bronchial tree; in the second, it was grossly disproportionate, the lower-lobe bronchi and the origins of bronchiectatic segments showing an abrupt collapse while the distal dilated segments remained widely patent.

To ascertain whether a relationship existed between dynamic activity of bronchi and the severity of disease morphologically, roentgenograms made at the time of cinebronchography were reviewed and the type of bronchiectasis was classified in each case, independent of knowledge of the bronchial dynamics. The multiplicity of classifications of the different forms of bronchiectasis is confusing, and it was decided to use that suggested by Reid⁶ in 1950, which separates the three forms of the disease into the more or less discrete morphologic entities that they appear to be both roentgenologically and pathologically: (a) cylindrical or fusiform, (b) varicose or beaded, and (c) cystic or saccular. As described by Reid, the *cylindrical* type presents in bronchi that are regular in outline and have only a moderate increase in diameter, usually with little associated

parenchymal destruction. The *varicose* type gives rise to more bronchial dilatation and to local constrictions that cause beading and irregularity in bronchial outline, in most cases with a greater degree of parenchymal destruction. In the *cystic or saccular* form, dilatation increases progressively towards the periphery so that the terminal portion of the bronchus has a ballooned outline; the cystic spaces are blind sacs and commonly are subpleural, indicating a severe degree of parenchymal destruction and fibrosis.

When the 20 bronchograms were classified on this basis and compared with the relative bronchial measurements (Table 1), it became clear that the morphologic classification of cylindrical bronchiectasis coincided exactly with the dynamics of the first group of cases, and that with one exception the classification of varicose and cystic bronchiectasis correlated with the dynamics of the second group. The exception (Case 20) had severe cystic disease of the left lower lobe and lingula, but her bronchial dynamics were well within the range of Group 1. More will be said of this patient later.

In Table II are listed the *average* inspiratory and expiratory calibers of each of the three bronchial segments according to their morphologic group (columns 3, 5 and 7), and the *average* percentage reduction in caliber of each division (columns 4, 6 and 8). The difference between the cases in Group A and those in Groups B and C can

be readily appreciated. The only significant difference between the cases of varicose (B) and cystic (C) bronchiectasis is in the reduction in caliber of the bronchiectatic spaces, amounting to 17 per cent and 7 per cent, respectively. Thus, although it may be convenient to subdivide the more severe grades of bronchiectasis into varicose and

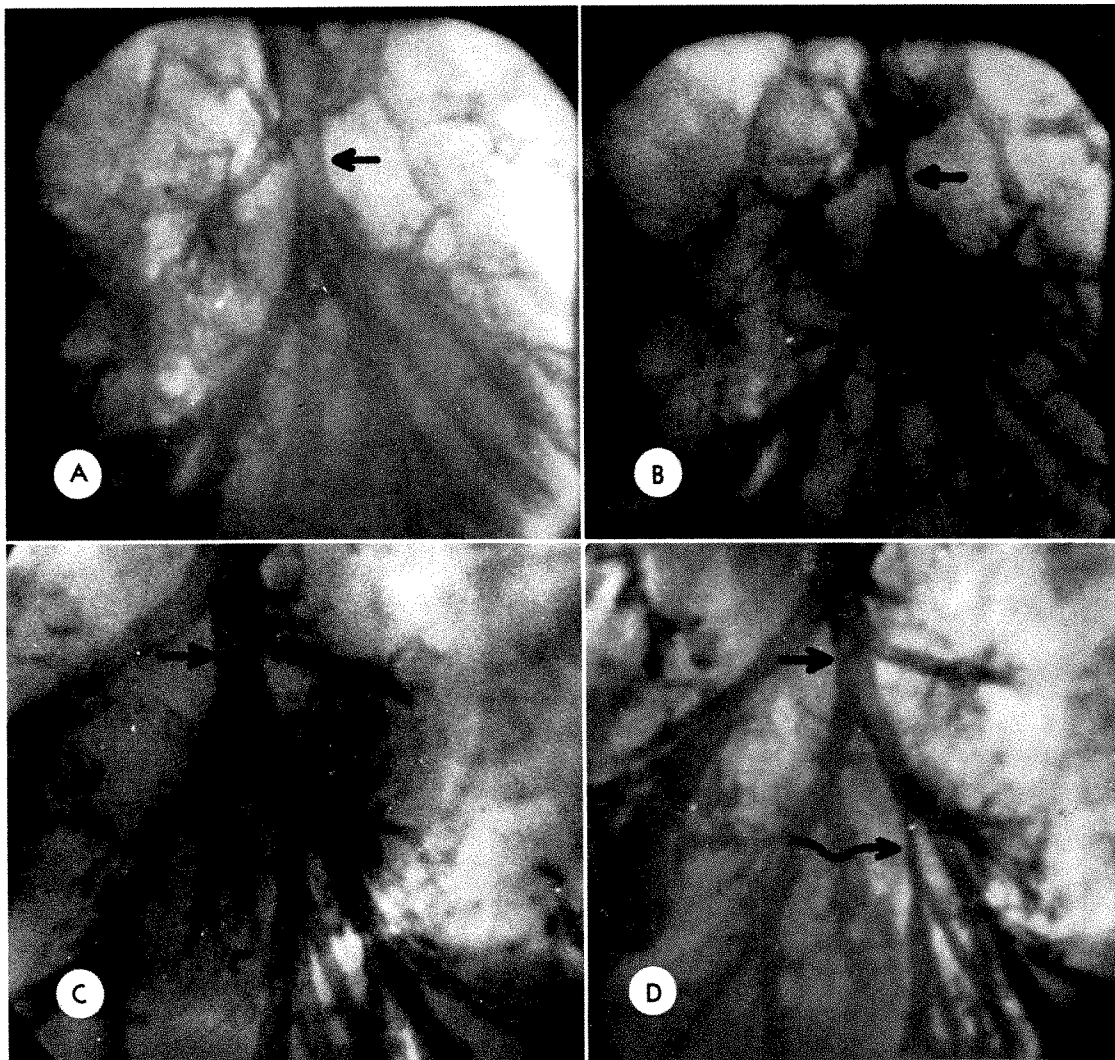


FIG. 3. Case 18 and 19. *Varicose bronchiectasis*. Representative cinefluorographic frames of both bronchial trees of a patient with bilateral disease. A and B were made in full inspiration and cough sequences in the *left* bronchial tree (Case 19) and C and D from similar sequences in the *right* (Case 18). In A and B the main bronchus to the left lower lobe (arrows) has collapsed on cough to 21 per cent of its inspiratory caliber, while the segmental origins and bronchiectatic segments have shown little change. In C and D, the right lower-lobe bronchus (straight arrows) has reduced by a normal 37 per cent, but the origin of one of the basal bronchiectatic segments (curved arrows) has collapsed by 67 per cent. These examples illustrate the variation in dynamics which may occur in different portions of the bronchial tree of the same patient. Compare these cinefluorographic frames with the manometric results obtained on this patient as shown in Figure 7.

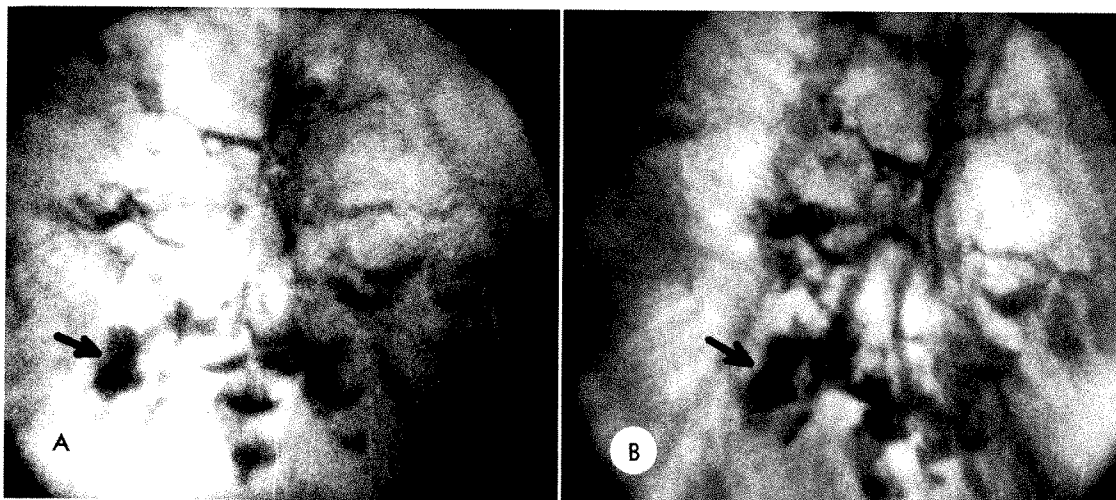


FIG. 4. Case 9. *Cystic bronchiectasis*. Representative cinefluorographic frames in full inspiration (A) and cough (B). The main bronchus to the lower lobe does not reproduce well but on the original film showed a reduction in caliber of 74 per cent from maximal inspiration to cough. Thus, disproportionate collapse of proximal bronchi led to a trapping of air, contrast material and secretions in the bronchi distal to them, manifested cinefluorographically by a failure of the cystic spaces to undergo any change in caliber (arrows).

cystic types morphologically, their functional behavior is so similar that they might well be considered as a single group insofar as dynamics are concerned.

Reference to Table I will show that 5 of the 8 patients with cystic disease exhibited no change whatever in the diameter of their bronchiectatic spaces on coughing. Although a slight change in the shape of the sacs was frequently observed, often associated with an alteration in position of the upper layer of contrast medium, the actual maximal diameter of the sac did not alter

despite forceful expiratory effort (Fig. 4, A and B). The notable exception among the patients with cystic disease (Case 20) showed a remarkable collapse of bronchiectatic spaces on forced expiration and during cough, amounting to an average of 53 per cent of inspiratory caliber (Fig. 5, A and B). This reduction in caliber, which was greater than in any other patient in the series, created a rather striking cinefluorographic effect, spaces measuring 15 mm. in diameter collapsing by over 50 per cent in response to cough. In contrast to the other

TABLE II
AVERAGE MEASUREMENTS OF 3 BRONCHIAL DIVISIONS IN CYLINDRICAL,
VARICOSE, AND CYSTIC BRONCHIECTASIS

1	2	3	4	5	6	7	8
Group	No. of Cases	Lower-lobe Bronchus		Segmental Origins		Bronchiectatic Segments	
		Average Diameter Insp./Exp. (mm.)	Average Reduction in Caliber (%)	Average Diameter Insp./Exp. (mm.)	Average Reduction in Caliber (%)	Average Diameter Insp./Exp. (mm.)	Average Reduction in Caliber (%)
A	5	10.4/6.1	42	6.7/4.4	34	8.3/4.9	41
B	8	10.7/4.2	60	7.9/3.0	61	9.0/7.5	17
C	7	8.8/2.9	67	5.9/2.3	60	14.8/13.8	7

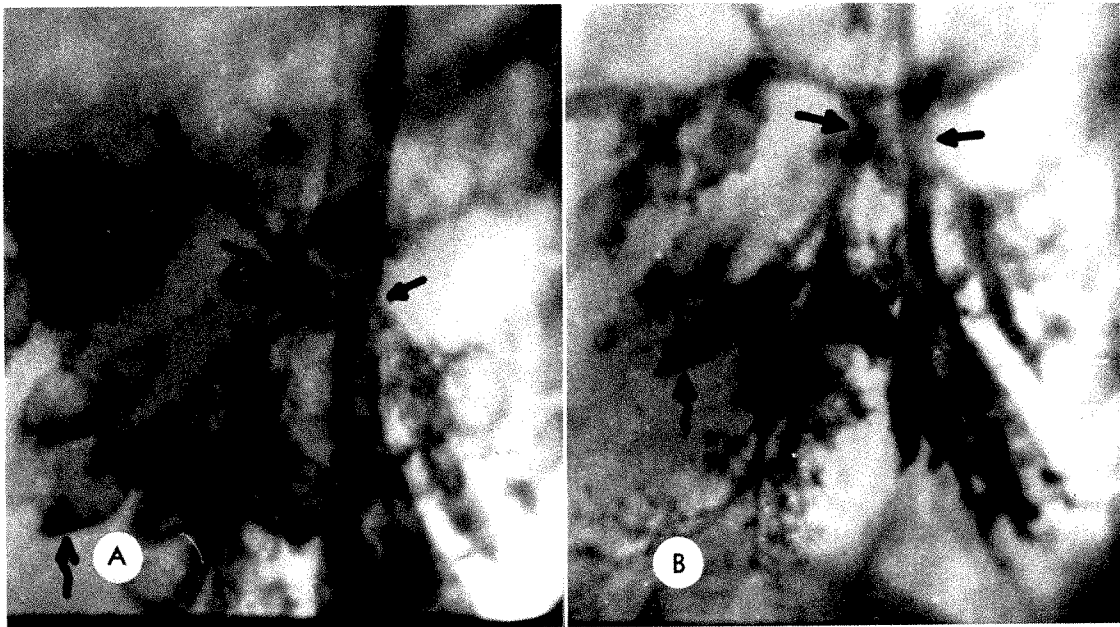


FIG. 5. Case 20. *Cystic bronchiectasis*. Representative cinefluorographic frames showing the maximal caliber on inspiration (A) and the minimal caliber on cough (B). The proximal large bronchi (straight arrows) and their segmental origins all underwent a normal reduction in caliber on coughing (see Table 1), with the result that flow of air and contrast material from the peripheral bronchiectatic segments was not obstructed. The cystic spaces were thus able to undergo a considerable reduction in caliber (curved arrows). Compare with Case 9 in Figure 4, A and B.

cystic cases, it is to be noted that this patient's lower-lobe bronchus and bronchial origins showed a caliber reduction on forced expiration which was within normal limits.

It will be noted from Table 1 that Cases 15, 16 and 17 possessed exceptionally narrow lower-lobe bronchi compared with those of most other patients in the series, although their bronchiectatic spaces were of large caliber. These 3 patients were rather small women, and their lungs and bronchial trees generally were smaller than average.

In the varicose and cystic cases, collapse of the lower-lobe bronchi and of the origins of the bronchiectatic segments appeared to occur simultaneously, at least within the limits of timing imposed by the frame speeds commonly used.

MANOMETRY

Figures 6, 7 and 8 show representative bronchial pressures in bronchiectatic segments and at other levels in the tracheo-

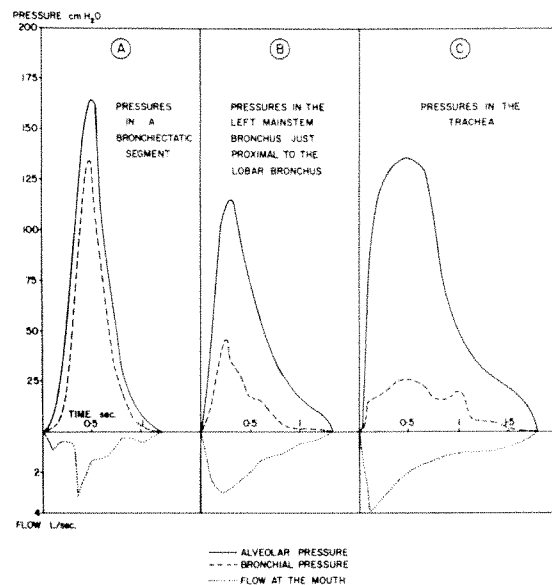


FIG. 6. Case 14. *Cylindrical bronchiectasis with normal bronchial dynamics*. Alveolar pressure, bronchial pressure, and flow at the mouth, during forced expiration. (A) Bronchial pressure catheter in a bronchiectatic segment in the left lung. (B) Bronchial pressure catheter in the left main-stem bronchus. (C) Bronchial pressure catheter in the trachea.

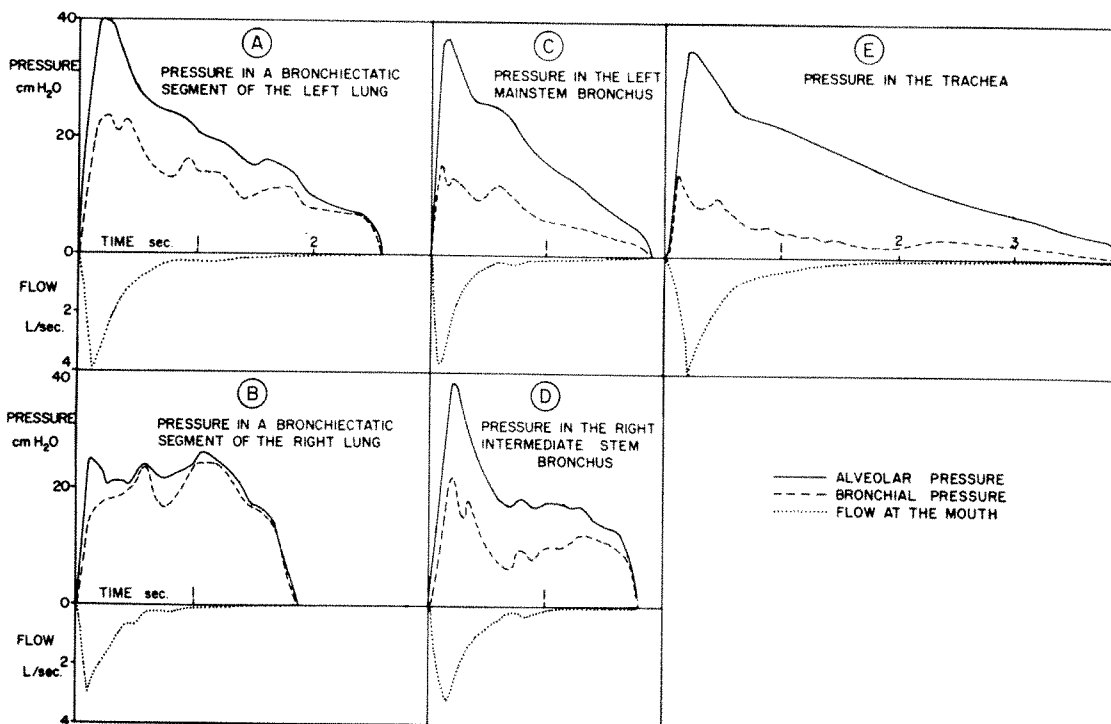


FIG. 7. Case 18 and 19. *Varicose bronchiectasis*. Alveolar pressure, bronchial pressure, and flow at the mouth, during forced expiration. (A) Bronchial pressure catheter in a bronchiectatic segment in the left lung. (B) Bronchial pressure catheter in a bronchiectatic segment of the right lung. (C) Bronchial pressure catheter in the left main-stem bronchus. (D) Bronchial pressure catheter in the right intermediate-stem bronchus. (E) Bronchial pressure catheter in the trachea. Compare with the cinefluorograms on this patient illustrated in Figure 3, A-D.

bronchial tree in a case from each of the three morphologic groups.

In Figure 6 are recorded the pressures in a bronchiectatic segment, in the left main-stem bronchus and in the trachea in a patient with cylindrical bronchiectasis (Case 14). These pressures are shown in relation to alveolar pressure and flow at the mouth. In normal subjects, the pressures in segmental bronchi are approximately equal to pleural pressure no matter how high that pressure rises, and are thus very close to alveolar pressure.⁴ The pressures in the bronchiectatic segment of this patient may, therefore, be considered as normal. Similarly, the pressures at the other levels of the tracheobronchial tree are normal.

Figure 7 shows the results in both lungs in a patient with varicose bronchiectasis (Case 18 and 19). On the left side, pressure within the bronchiectatic space was abnormally low, being slightly more than half

that in the alveolus. On the right side, however, pressures were normal.

Figure 8 shows the pressures in a bronchiectatic sac, in a lobar bronchus, and in the trachea, of a patient with cystic disease (Case 16). In this patient, whereas pressures within the sacs were the same as in a normal subject for the same bronchial generation, those in the lobar bronchus proximal to the area of marked expiratory collapse were *lower* than normal.

DISCUSSION

Although it is still not certain why there are differences in dynamic activity of the bronchial tree in cylindrical and in varicose or cystic types of bronchiectasis, certain aspects of bronchial dynamics are well enough known so that certain tentative conclusions may be drawn.

Fry and Hyatt² described very lucidly the interacting forces within the thorax

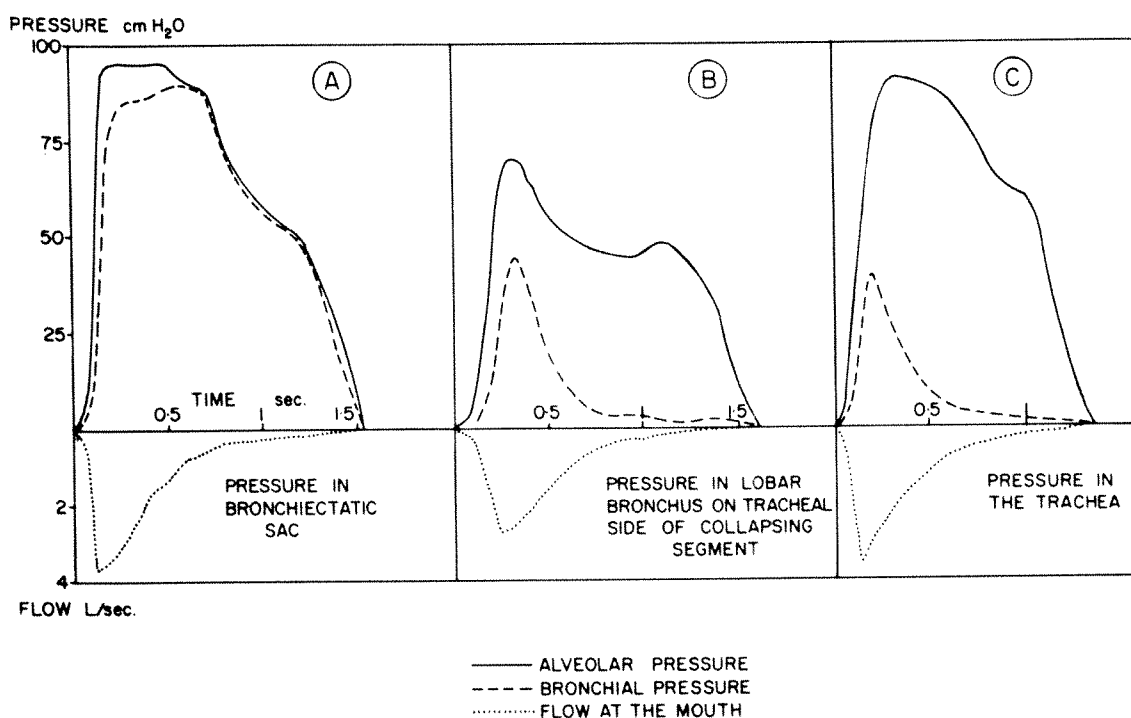


FIG. 8. Case 16. *Cystic bronchiectasis with lobar bronchial collapse*. Alveolar pressure, bronchial pressure, and flow at the mouth, during forced expiration. (A) Bronchial pressure catheter in a bronchiectatic sac. (B) Bronchial pressure catheter in the lobar bronchus just downstream from collapsing segment. (C) Bronchial pressure catheter in the trachea.

that affect bronchial caliber during respiration. They showed that alteration in bronchial caliber is due to the difference in pressure across the bronchial wall, a differential that is related, in part, to pleural pressure, to air flow through the bronchus, and to resiliency of the bronchial wall. There are two obvious differences between the cylindrical and the varicose or cystic types of bronchiectasis, one dynamic and the other morphologic. It is probable that both contribute in some measure to the effects demonstrated, although, as will be shown, the former appears to predominate.

MORPHOLOGIC CHARACTERISTICS

Since the amount of parenchymal destruction and fibrosis increases with the severity of the bronchiectasis, it may be assumed that the reduction in air flow through the diseased bronchi will be most marked in the cystic cases. There is good reason to believe that such air-flow restric-

tion, by reducing pressure within the airway, can lead to distal bronchial closure on forced expiration. Evidence to this effect was supplied recently by our discovery at bronchography of a blind supernumerary bronchus arising from the inferior aspect of the right intermediate-stem bronchus in a patient without other significant bronchial abnormality (Fig. 9, *A* and *B*). This anomalous bronchus, which measured approximately 6 cm. in length, had no demonstrable communication with the parenchyma of the lung, being directed medially and inferiorly along the mediastinal border. On forced expiration and cough during cinefluorography, this bronchus was seen to collapse completely, presumably because there was no air flow from distal parenchyma to maintain high intraluminal pressure. In fact, air flow, by producing intrabronchial pressure, is a major factor in the prevention of airway closure in normal segmental and lobar bronchi.

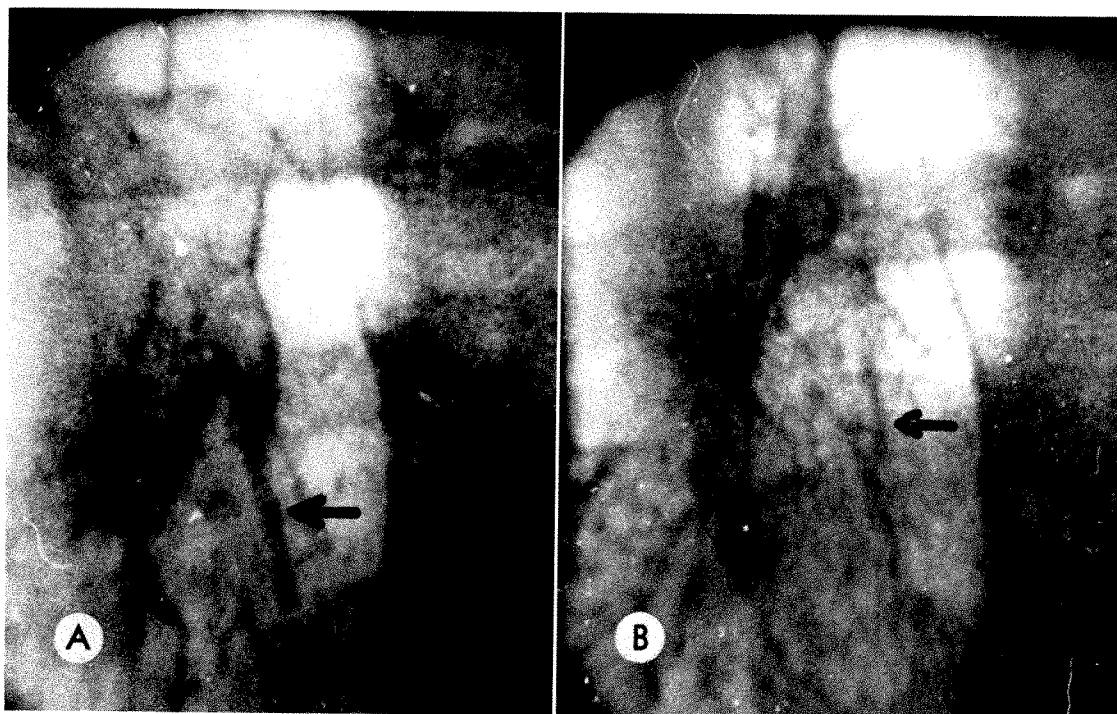


FIG. 9. Representative cinefluorographic frames in maximal inspiration (*A*) and cough (*B*) from a cine-bronchogram in which a blind supernumerary bronchus is seen to arise from the inferomedial aspect of the right intermediate-stem bronchus (arrows). This supernumerary bronchus passed medially along the mediastinal border and possessed no identifiable lung parenchyma leading to it. Almost complete obliteration of the lumen of the bronchus occurred on coughing, illustrating the fact that, in the absence of proximal obstruction, a bronchus will almost completely evacuate its contents on cough or forced expiration, despite no functioning parenchyma supplying it. Compare with cases illustrated in Figures 4, *A* and *B*; and 5, *A* and *B*.

Similarly, it might be thought that the fibrosis encircling the peripheral sacs in cystic, and to a lesser extent in varicose, bronchiectasis might effectively act as an encasement, preventing their collapse. Fry and Hyatt² pointed out, however, that the elastic and fibrous tissues, of the lung normally exert a dilating effect on the bronchial tree. Although an increase in fibrous tissue might be expected to accentuate this dilating effect, it is a dynamic force and should not act as a prohibitory agent in preventing closure. In addition, although the bronchial walls in severe bronchiectasis might be thought to be thickened and rigid, they are in fact often thin and flaccid, particularly when cystic, so that closure should not be impeded for this reason. Thus, from a morphologic point of view, there is little reason to suspect that the peripheral paren-

chymal changes in the lung exert more than a minor influence in preventing closure of dilated bronchi.

It is probable, however, that morphologic change in the structure of the bronchial wall may be a major contributing factor. Wright¹⁰ described pathologic changes in the segmental bronchi of patients with chronic bronchitis and emphysema that could conceivably result in abnormal flaccidity. He noted an increase in transparency of peripheral bronchial walls, with reduction in the size and number of cartilage elements and in the amount of smooth muscle and fibrous tissues. The larger bronchi showed similar though less-marked changes; in addition, they possessed elliptic rather than round lumina and collapsed more easily on external manual pressure than did normal bronchi. De-

iciency in cartilage has been described by Williams and Campbell⁹ in 5 children with generalized bronchiectasis, their evidence suggesting that the deficit was developmental rather than acquired. It is clear that further investigation is needed to clarify the relationship between bronchial-wall "softening" and altered dynamics, not only in bronchiectasis but also in chronic bronchitis and emphysema; however, sufficient evidence has accrued to suggest that morphologic change in the structure of the bronchial wall is primarily responsible for the derangement in dynamics.

BRONCHIAL DYNAMICS

It has been shown by cinebronchographic and other methods that the main bronchus to the lower lobe tends to collapse in forced expiration in patients with chronic bronchitis and emphysema. Using a combined cinebronchographic-manometric technique, Macklem *et al.*³ recently established that, coincident with this expiratory collapse, there occurs a sharp rise in intrabronchial pressure distal to the collapsing bronchus and a wide pressure drop across it, neither of which occurs in the normal bronchial tree. Associated with the sharp rise in intrabronchial pressure is a prompt decrease in air flow, despite a continuing increase in intrapleural or driving pressure. These observations have shown conclusively that the central bronchi exert a significant influence in expiratory air-flow obstruction in these diseases.

In the present series, bronchial pressure measurements have demonstrated that in cylindrical and in cystic bronchiectasis, the pressures within the bronchiectatic spaces are high during forced expiration. Pressures within a bronchus during expiration are dependent upon many factors, among which the flow rate through the bronchus and the amount of obstruction downstream from it (towards the mouth) are the most important. In cylindrical bronchiectasis, it has been shown that the alveoli subtended by the bronchiectatic spaces function normally; therefore, one would expect that the

flow through these spaces also would be normal and, thus, that the pressures inside them would be high. In cystic bronchiectasis, on the other hand, the bronchiectatic spaces are blind sacs, so that the only flow through them must come from emptying the sacs themselves. Since it has been shown that in the majority of cases the sacs do not empty, flow must be negligible. In this circumstance, the *only* way in which pressure within them can rise is for the sacs to become almost totally obstructed during expiration: the expiratory collapse of the origins of these sacs and of the lobar bronchus seen cinefluorographically reveals that this is indeed the case. Although one would expect the pressures to be low and the sacs to collapse in exactly the same manner as the blind accessory bronchus described earlier, the pressures remain high and the sacs do not empty, because of expiratory collapse of airways downstream. Although pressures in cylindrical and in cystic bronchiectatic spaces are high, this is so for entirely different reasons: in the former they are high because flow is high, and in the latter because of obstruction to flow.

In varicose bronchiectasis, there is more parenchymal destruction in the region of the bronchiectatic spaces than in the cylindrical type, but the sacs are not blind. One might expect, therefore, that flow through them would be reduced, but not to the same degree as in the cystic forms. The pressure within would be reduced by air-flow restriction, an effect that might be counteracted by the greater expiratory collapse than occurs in cylindrical bronchiectasis. Thus the pressures in varicose bronchiectatic spaces should reflect two factors—a reduction in air flow resulting from surrounding parenchymal destruction and the degree of expiratory collapse of airways downstream. One of the patients studied (Case 18 and 19) presumably demonstrated predominance of both abnormalities (Fig. 3, A and 7). On the left side, pressures in bronchiectatic spaces were lower than normal and it is reasonable to suppose that the effect of flow restriction predominated over

that of airway collapse on this side; in the right bronchial tree, pressures distally were high, and on this side airway collapse presumably predominated over the effect of flow restriction.

These results are important in considering the efficiency of cough in bronchiectasis. Cough, along with ciliary action, empties the bronchial tree of its secretions. To be effective, there must be a high velocity of air in the bronchi as well as an efficient ratio of particle size to tube diameter. The velocity of air in a tube is the flow divided by the cross-sectional area. Normal airway narrowing, by increasing velocity and improving the ratio of particle size to tube diameter, is a very important feature of cough. However, in bronchiectasis of any type, not only must the velocity be considerably less than normal but also there must be a less efficient ratio of particle size to tube diameter because the tubes are dilated. In any form of bronchiectasis, therefore, cough is seriously impaired. In the cylindrical type, maintenance of normal flow, coupled with reduction in caliber, allows cough to eliminate some secretions. In saccular disease, on the other hand, flow from the cystic spaces must be negligible. In the absence of flow, the only way the sacs can evacuate their contents is by their collapse; since this is prevented by closure of the larger airways downstream, cough can be of no assistance in the elimination of secretions. Retention of purulent secretions, in turn, must contribute significantly to both progression of the bronchiectatic process and the repeated pulmonary infections that characterize this disease. Thus, airway collapse is not merely a finding of academic interest—it is a major factor contributing to the morbidity of bronchiectasis.

One other aspect of some practical importance in the demonstration of bronchial dynamics in bronchiectasis lies in the choice of site for surgery when disease is present bilaterally. One of our patients, a 30-year-old woman with bilateral lower-lobe varicose bronchiectasis (Case 18 and 19) is

a case in point. Her disease morphologically was of about the same severity on the two sides (Fig. 3, *A-D*). Reference to Table 1 will show that, on forced expiration, her *left* lower-lobe bronchus collapsed to one fifth of its inspiratory diameter, the peripheral bronchiectatic spaces showing no change whatever in caliber. On the *right* side, the lower-lobe bronchus reduced by only 37 per cent, and although there was a 67 per cent collapse of at least one segmental origin, the peripheral varicose spaces reduced by 20 per cent. Since manometry confirmed the superiority of function of the right lower lobe compared with the left (Fig. 7), it was considered advisable to remove the left lower lobe first, and this was in fact done.

RELATIONSHIP TO CHRONIC BRONCHITIS

As has been pointed out, central bronchial collapse is presumably due to softening of the bronchial wall. It is not likely to be due to the bronchiectasis *per se*, since bronchiectasis is predominantly a disease of segmental and peripheral airways. Since collapse of a similar nature is seen also in chronic bronchitis and emphysema, it is highly likely that the common denominator in the three diseases is bronchitis and that this is the process leading to softening of the wall. Apart from loss of bronchial tapering, a sign which is of no value in bronchiectasis, the only convincing morphologic evidence for the presence of chronic bronchitis bronchographically is dilated mucus glands, and such evidence appears in no more than 50 per cent of cases.⁸ Visible mucus-gland filling was present in 6 patients in the present series, 2 being in the varicose group, 4 in the cystic and none in the cylindrical. While such numbers hardly constitute a statistically significant quantity, they lend some support to the hypothesis that chronic bronchitis may be the pathogenetic factor leading to bronchial collapse in bronchiectasis and other obstructive airway diseases.

In this regard Case 20 is of unusual interest. She was the only patient with cystic bronchiectasis in whom significant reduc-

tion in cyst caliber occurred on coughing (Fig. 5, *A* and *B*). This reduction in caliber, amounting to 53 per cent of full inspiratory diameter, was not associated with disproportionate collapse of the larger airways—a combination of circumstances that, as has been noted, should allow a more efficient cough than the other patients with cystic disease could perform. It is also to be noted that this patient, the youngest in the series, was only 16 years of age. It is tempting to try to relate the factor of age to the influence of chronic bronchitis in the pathogenesis of central bronchial collapse. It might be suggested that, at 16 years, it would be unlikely for chronic bronchitis to have developed to a sufficiently severe degree to give rise to flaccidity and collapse. Thus, it is interesting to compare this patient with the next-youngest patient in the series, Case 17, a 21-year old woman with moderately severe cystic disease of her left lower lobe. This woman's lower-lobe bronchus and segmental origins collapsed to 50 and 66 per cent, respectively, with no alteration in diameter of the bronchiectatic spaces. Extensive mucus-gland filling at bronchography indicated the presence of severe chronic bronchitis. It is open to conjecture whether the 5-year difference in age of these 2 patients might be related to the presence of chronic bronchitis in one and its absence in the other.

SUMMARY AND CONCLUSIONS

1. It is known that chronic bronchitis and emphysema are characterized by disproportionate collapse of larger airways on forced expiration or cough. The possibility that a similar derangement might occur in bronchiectasis stimulated an investigation into the characteristics of bronchial dynamics in this disease and into a possible relationship between the disturbance found in bronchiectasis and in chronic bronchitis and emphysema.

2. A total of 20 bronchograms of 17 patients was studied cinefluorographically. Measurement was made of the transverse

diameter of at least 3 bronchial segments in full inspiration and in forced expiration or cough—the lobar bronchus, the origin of one or more of the bronchiectatic segments, and the bronchiectatic segments themselves at their point of greatest dilatation. In 4 cases, manometry and cinebronchography were carried out concurrently, allowing simultaneous assessment at any given moment of the caliber of a bronchus, the pressure within it, pleural pressure and air flow at the mouth.

3. Variations in bronchial measurements and pressures allowed division of the 20 cases into three fairly distinct groups:

Group A. Dynamics followed a normal pattern, cough producing a roughly proportionate reduction in caliber down the length of the bronchial tree, including the bronchiectatic segments. Intrabronchial pressures were high and within normal limits. This group comprised all 4 cases of cylindrical bronchiectasis and one of advanced cystic disease in a 16-year-old girl.

Group B. Reaction of diseased bronchial segments was disproportionate, cough producing collapse of the lobar bronchi or segmental origins, with concomitant maintenance of caliber of bronchiectatic segments to almost inspiratory levels. Pressures within bronchiectatic segments on forced expiration were usually but not always high. In this group, which comprised all 8 cases of varicose bronchiectasis, disturbance in bronchial dynamics and pressures was intermediate between that of the other two groups, being generally less severe than in Group C.

Group C. Collapse of lobar bronchi and of segmental bronchial origins on cough was striking and was associated with little or no change in caliber of bronchiectatic segments. Intrabronchiectatic pressures were high. Seven of the 8 cases of cystic disease made up this group.

4. Pressures within bronchiectatic spaces on forced expiration and during cough were high in cylindrical and in cystic disease, but for different reasons. In the former, the preservation of abundant functioning pa-

renchyma leading to the involved segments, in the presence of normal dynamics, allows a high air flow which, in turn, produces high intrabronchial pressure. In cystic disease, functioning parenchyma is negligible so that the only source for air flow must be from the sacs themselves; since emptying of the sacs is effectively prevented by collapse of bronchi downstream, air flow is minimal and intrabronchial pressure high.

5. Certain conclusions of practical importance may be derived from these observations. To be efficient, cough must be associated with a high air velocity and with an effective ratio of particle size to tube diameter. In bronchiectasis of any form, both of these conditions are suboptimal, so that cough is relatively inefficient in ridding involved segments of their secretions. In cystic and varicose bronchiectasis, the situation is much worse than in cylindrical disease: not only is air flow and, therefore, velocity negligible, but since the spaces remain dilated despite vigorous expulsive effort, the ratio of tube diameter to particle size must cause much interference with the cough mechanism. Thus, purulent secretions are retained, with the inevitable contribution such retention must make to progression of the bronchiectatic process and to the repeated pulmonary infections that characterize the disease. Central airway collapse must, therefore, be regarded as a major factor contributing to the morbidity of bronchiectasis.

6. The altered dynamics in varicose and cystic bronchiectasis strongly resemble those in chronic bronchitis and in emphysema. Present evidence suggests that chronic bronchitis is the common denomi-

nator in the production of disturbed bronchial mechanics in these three diseases.

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PULMONARY MUSCULAR HYPERPLASIA*

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PULMONARY muscular hyperplasia is a disease of unknown etiology characterized by a marked increase in the amount of smooth muscle tissue in the lung. It is a progressively fatal condition found in both sexes in the middle age group. The true incidence is not yet known, but approximately 30 cases have been reported in the world literature. We have had the unique opportunity to follow 11 cases (Table 1) roentgenologically with Dr. William Fraimow and Dr. Richard T. Cathcart³ of the Barton Memorial Division of Jefferson Medical College Hospital, a referral center for chest diseases. The chest findings and the pathophysiology of this disease to our knowledge have not been described in the radiologic literature. It is important for roentgenologists to be aware of this entity and to include it in the differential diagnosis of progressive interstitial fibrosis.

Increased amounts of smooth muscle in the lung have long been reported in patients with chronic pulmonary infection. Patients with bronchiectasis, abscess formation, tuberculosis, unresolved pneumonitis, and chronic chylothorax have localized areas of smooth muscle hyperplasia in conjunction with the chronic infection.⁵ It may also occur as part of the systemic disease, tuberous sclerosis.¹ The occurrence of a primary generalized smooth muscle hyperplasia disseminated throughout the lungs, however, is relatively uncommon.

The entity was first described by von Buhl⁸ in 1873 as muscular cirrhosis of the lung. Since that time, various names have been given to it, including bronchiolar emphysema, pulmonary myomatosis with microcyst formation, and muscular cirrhosis. Recently, as the pathologic appearance

has been clarified, it has been called pulmonary muscular hyperplasia.⁶

CLINICAL FEATURES

The majority of patients has presented a picture of gradually increasing shortness of breath, weakness, fatigue, cough, and weight loss. The cough has been nonproductive and is only partially controlled by opiates. There is increasing exertional dyspnea to the point of marked incapacitation and right heart failure. The clinical course has been progressively downhill. Severe exacerbation of symptoms occurs when there is a superimposed infection. Several patients were first seen when they were completely free of symptoms, but with time, the characteristic picture of pulmonary insufficiency supervened.

Most of the patients have demonstrated marked clubbing of the fingers. Frequently, there were rales on physical examination of the chest. Except for pulmonary function studies, laboratory tests have been of little value. Despite significant arterial oxygen unsaturation and clubbing, there has been no evidence of secondary polycythemia.

Roentgenograms are useful to follow the course of the disease. There is no known therapy of any consequence; one can only control the superimposed infection. Several patients have been treated with corticosteroids without apparent effect. The use of intermittent positive pressure breathing and bronchodilators has been of no value.

HISTOLOGY

The disease is characterized by dense masses of smooth muscle, fibrous, and

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TABLE I
SUMMARY OF CASES
PULMONARY FUNCTION STUDIES

Case	Age	Sex	Race	Evidence of Carcinoma	VC	MBC	O ₂ Sat.	O ₂ Sat. \bar{p} Exer- cise	pCO ₂	pH	
I	53	M	W	Anaplastic carcinoma	71	88	86	58	28	7.43	1
II	52	M	N		32	45	87		47	7.37	2
III	48	M	W	Clinical diagnosis of carcinoma	56	65					3
IV	28	F	N		45	88	96	78	36	7.42	4
V	54	F	W	Cytology suspicious of carcinoma	50	96	83	73	43	7.39	5
VI	34	F	W		46	63	90	84	38	7.48	6
VII	45	F	W		87	91	94	76	40	7.39	7
VIII	40	F	N		41	65	91	64	36	7.43	8
IX	48	M	W		86	86	95	85	45	7.38	9
X	58	F	W	Alveolar carcinoma	42	51	94	73	36	7.44	10
XI	59	M	W	Severe squamous metaplasia							11

VC=vital capacity (% of normal).

MBC=maximum breathing capacity (% of normal).

O₂ Sat.=arterial O₂ saturation at rest (normal 96%).

O₂ Sat \bar{p} exercise=arterial O₂ saturation after exercise (normal 100%).

pCO₂=arterial pCO₂ (mm. Hg) (normal 40 mm. Hg).

pH=arterial blood pH (normal N 7.43).

elastic tissue disseminated throughout the lungs. Interspersed in these areas are large irregular cystic cavities which may vary in size and shape. These cystic cavities represent dilated bronchioles and in some instances alveoli. Often there are bands of smooth muscle fibers surrounding the cyst in addition to the marked fibrosis. Muscle bundles may be noted in peri-alveolar, peri-bronchial, interlobular, and interstitial septa. The proliferation of smooth muscle may be so marked in some areas as to be tumor-like in appearance.

The marked increase in muscle components, together with the interstitial fibrosis, results in greatly thickened alveolar septa, even in areas where the pulmonary architecture is not completely distorted. The thickening of the alveolar septum gives rise to the basic physiologic defect in this disease, *i.e.*, the difficulty in diffusion of oxygen from the alveolus to the pulmonary capillaries.⁴ This alveolar capillary block syndrome has been noted before in the presence of granulomatous and neo-

plastic disease as well as in idiopathic fibrosis. The combination of the diffuse increase in the interstitial fibrosis as well as in smooth muscle makes gaseous exchange difficult and leads to arterial oxygen unsaturation.

PULMONARY FUNCTION STUDIES

Most patients show a decrease in functioning lung volume manifested by a reduction in the vital capacity. In addition, there is generally a severe diminution in ventilatory ability as evidenced by decreased maximum breathing capacity. However, in all patients, the 3 second timed vital capacity is generally within normal limits.

Retarded gas diffusion and oxygen absorption is the characteristic physiologic lesion of pulmonary muscular hyperplasia.³ In all patients there is a significant degree of arterial oxygen unsaturation. In addition, there is a marked drop in arterial oxygen saturation after exercise. Since carbon dioxide diffuses much more rapidly than

oxygen, this is not accompanied by an elevation of the $p\text{CO}_2$.

The degree of oxygen unsaturation does not reflect the decreased ventilatory capacity. In fact, it seems to be an independent variable since several patients had marked oxygen unsaturation with normal ventilatory capacity. While the spirographic pattern is primarily restrictive, there generally is a preservation of ventilatory ability until late in the course of the disease.

ROENTGENOGRAPHIC FINDINGS

Periodic chest roentgenograms are an important means of following the progress of the disease. In all our patients there is diffuse lung involvement with a fine reticular pattern throughout both lung fields. Occasionally, there are what appear to be tiny nodular densities. Interspersed are small areas of radiolucency which produce a honeycomb type of pattern. Some Scandinavian authors felt that this picture was so characteristic they were willing to make the diagnosis on the basis of laminagrams.⁷ We feel, however, that one cannot distinguish between the multiple causes of diffuse interstitial fibrosis by roentgenologic appearance alone.

Whereas the parenchymal lung changes are hallmarks of this disease, several of our patients demonstrated lymphadenopathy on the chest roentgenograms. Hilar enlargement and occasionally even paratracheal lymphadenopathy were associated with the lung changes. This may be an important clue to the diagnosis since lymphadenopathy is not seen with other types of interstitial fibrosis except sarcoidosis.

An important feature worthy of special comment in many of our patients has been the incidence of carcinoma of the lung. We have had 2 patients with histologically proven carcinoma and 1 patient who died without autopsy with clinical evidence of carcinoma. A fourth patient had cells which were thought to indicate neoplasm in a bronchoscopic aspirant. This high incidence in such a small sample makes it highly unlikely that this is coincidental. The radiologist should be aware of this

relationship and view with suspicion any area of consolidation superimposed upon a primary disease process which does not resolve promptly with antibiotic treatment.

The history can be of distinct help to the radiologist in the differential diagnosis of this group of diseases. The presence and duration of chest symptoms will rule out many acute processes. A history of exposure to noxious dusts is mandatory when considering the possibility of pneumoconiosis. Skin tests and sputum analysis will aid in the diagnosis when the changes are caused by fungi or tuberculosis. Chronic interstitial edema from long standing congestive heart failure may mimic the roentgenologic appearance of pulmonary muscular hyperplasia. The presence of left ventricular enlargement and occasionally pleural effusions will point to primary cardiac disease. Extensive spread of carcinomatosis by the pulmonary lymphatics is usually soon apparent clinically. An understanding of the altered physiology is also useful. Pulmonary muscular hyperplasia must be included in the differential diagnosis of any patient with diffuse interstitial fibrosis.

Ultimately, the diagnosis must be made by biopsy. Even then pulmonary muscular hyperplasia can be confused with other diseases such as congenital cystic disease or chronic interstitial pneumonia, and errors may be made unless the pathologist is familiar with the entity and employs special histochemical stains for smooth muscle (Masson trichrome).

REPORT OF CASES

CASE 1 (Fig. 1, A-G). A 53 year old white male was admitted to Jefferson Medical College Hospital on August 22, 1955, because of exertional dyspnea and roentgen evidence of bilateral pulmonary infiltrations. The dyspnea had become increasingly severe for about 5 years. In the last 2 to 3 months, the patient had developed a dry cough. There was a past history of exposure to poisonous gas in World War I, which was followed by a disabling psychoneurosis. On physical examination, both fingers and toes were clubbed and slightly cyanotic. Rales were heard at the bases with some dullness to percussion. Roentgenograms of the chest re-

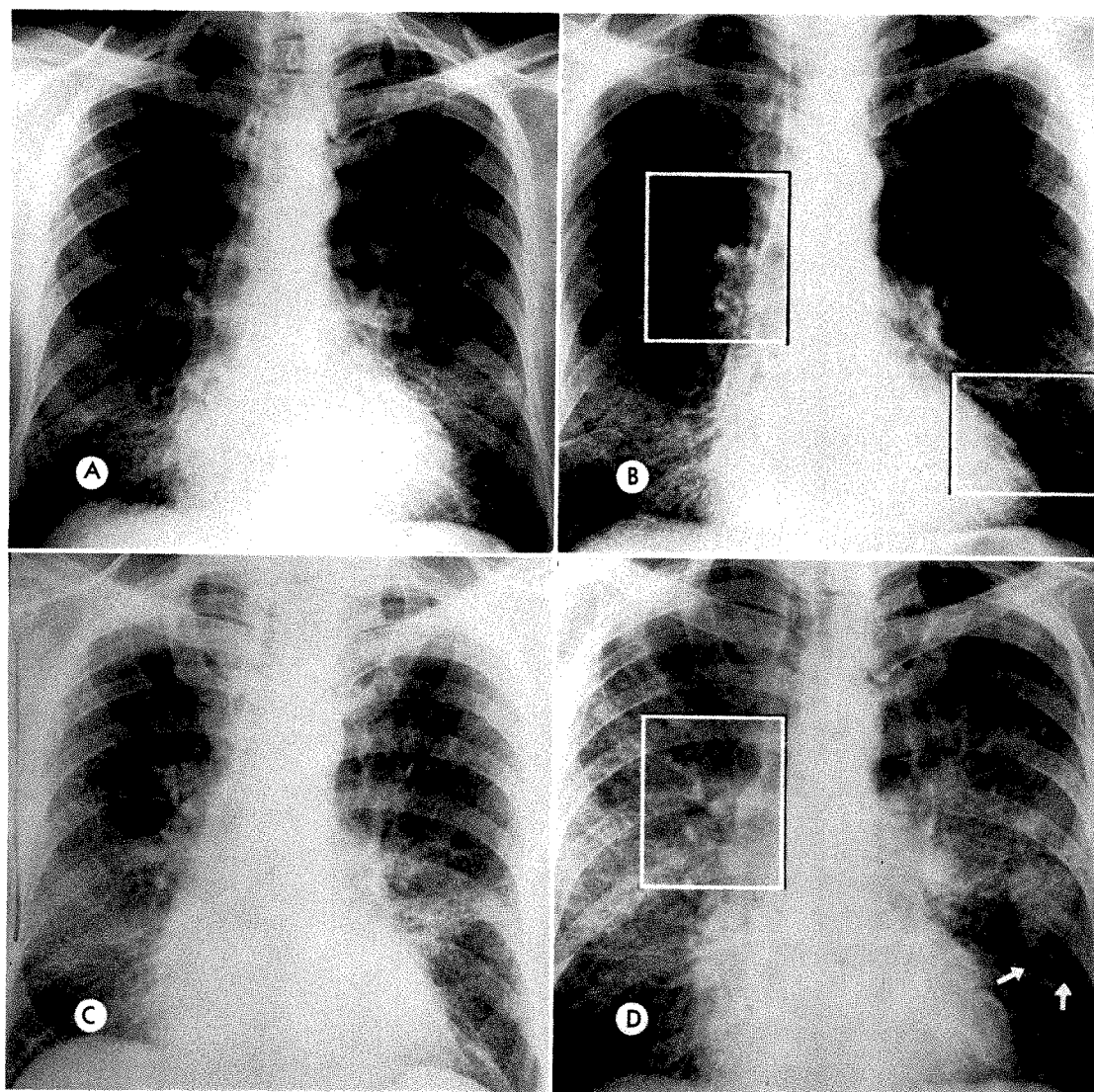


FIG. 1. Case 1. Male, aged 53. (A) 8-23-55: There is a fine bilateral reticular pattern throughout both lung fields most evident at the bases where there is greater volume of lung tissue. (B) 8-6-57: Gradual progression of the interstitial fibrosis. (C) 1-26-60: Marked progression. (D) 8-22-60: Further progression of the disease process. Note the development of a mass lesion in the left mid-lung field (arrows) and enlargement of the left hilus. Biopsy of this area revealed anaplastic carcinoma.

vealed a fine diffuse reticular pattern, more marked in the mid-portion and bases of the lung. All the laboratory studies were normal. Sputum was negative for tubercle bacilli, pathogenic organisms, or cytologic evidence of malignancy. Pulmonary function test showed an alveolar-capillary block. Lung biopsy demonstrated pulmonary muscular hyperplasia.

The patient was re-admitted 5 years later with increasing dyspnea and hemoptysis. Chest roentgenograms revealed slight progression of the previously described findings. A small addi-

tional area of density was noted in the periphery of the left mid-lung field. This area was biopsied under local anesthesia; anaplastic carcinoma was superimposed upon the pulmonary muscular hyperplasia. The patient died shortly thereafter.

CASE II (Fig. 2). A 52 year old Negro male was admitted to Jefferson Medical College Hospital on December 28, 1959 because of increasing exertional dyspnea and an 18 pound weight loss. He had a mild nonproductive

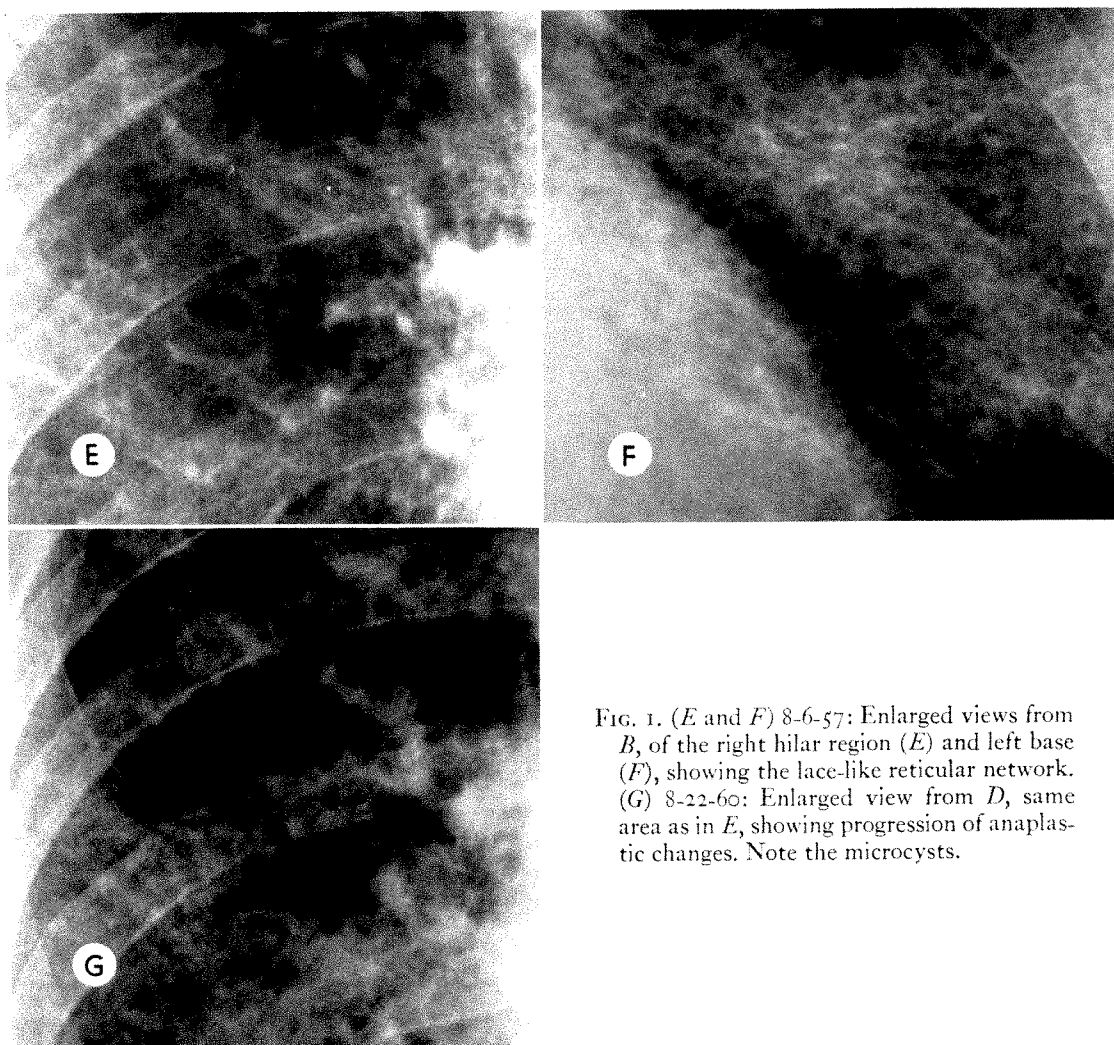


FIG. 1. (*E* and *F*) 8-6-57: Enlarged views from *B*, of the right hilar region (*E*) and left base (*F*), showing the lace-like reticular network. (*G*) 8-22-60: Enlarged view from *D*, same area as in *E*, showing progression of anaplastic changes. Note the microcysts.

cough, but denied the symptoms of respiratory disease. Two years previously he was informed of an abnormal survey chest roentgenogram; but since he had no symptoms, he neglected to obtain any follow-up care.

Physical examination revealed an elderly male in mild respiratory distress. There was slight clubbing of the fingers and toes. Basilar rales and rhonchi were heard in the chest. Laboratory tests were normal. Skin tests for fungus disease were negative; intermediate PPD was positive. Three sputum examinations were negative for acid fast bacilli on smear and culture. Pulmonary function studies showed evidence of both restrictive disease and alveolar-capillary block.

An intercostal lung biopsy was performed and



FIG. 2. Case 11. Male, aged 52. 5-19-60: Combined pattern of nodular and interstitial changes. The patient developed marked cor pulmonale.

the histologic diagnosis was pulmonary muscular hyperplasia.

The patient was re-admitted twice during the next year with progressively more severe dyspnea. Electrocardiograms showed evidence of cor pulmonale. In spite of prednisone and cardiac therapy, he rapidly decompensated and died with respiratory insufficiency.

CASE III (Fig. 3, *A* and *B*). A 48 year old white male was admitted to Jefferson Medical College Hospital on October 22, 1960 because of back pain and progressive severe dyspnea. For the past 6 years, the patient had had symptoms of wheezing, nonproductive cough, and gradually increasing shortness of breath. Chest roentgenograms taken at another hospital in 1954 showed increased bronchovascular markings. A bronchogram was reported as showing saccular bronchiectasis of both lower lobes and the right middle lobe. There was no history of weight loss or hemoptysis.

On admission, the patient had marked clubbing of fingers and toes, and bilateral inspiratory and expiratory wheezes and rales. Chest roentgenograms disclosed a right sided mass in the superior mediastinum and marked pulmonary fibrosis bilaterally. Bronchoscopy revealed a right upper lobe bronchus which was deformed and compressed by an extrinsic mass.

A lung biopsy was performed and the histologic diagnosis was pulmonary muscular hyperplasia. The patient died 1 month later at another hospital. The clinical diagnosis was carcinoma of the lung, but autopsy permission was refused.

CASE IV (Fig. 4, *A-D*). A 28 year old Negro female was admitted to Jefferson Medical College Hospital on November 8, 1960 with a 6 week history of cough, productive of yellow sputum. Six months prior to admission, the patient noted the gradual onset of mild dyspnea and a persistent cough. There was no history of weight loss, hemoptysis, or night sweats.

Physical examination was within normal limits except for fine inspiratory rales at the bases which did not clear with coughing. Laboratory studies, including cultures of gastric washings and sputum were negative. Chest roentgenograms demonstrated nodular increases in density bilaterally with multiple small cystic areas of radiolucency. Pulmonary function studies showed the presence of an alveolar-capillary block. A lung biopsy was reported as compatible with pulmonary muscular hyperplasia. The patient was placed on steroid therapy with apparently no improvement.

The patient was re-admitted to the hospital 2 years later with increasingly severe dyspnea, cough and hoarseness. Electrocardiograms showed evidence of myocardial ischemia. The patient was eventually discharged. Her condition was unchanged.

CASE V (Fig. 5, *A-D*). A 54 year old white female was admitted to Jefferson Medical College Hospital on March 27, 1961 because of 10 months of progressively increasing exertional dyspnea and clubbing of the nails. The patient had a chronic cough productive of white mucoid sputum. There was no history of hemoptysis, chills, fever, weight loss, or occupa-

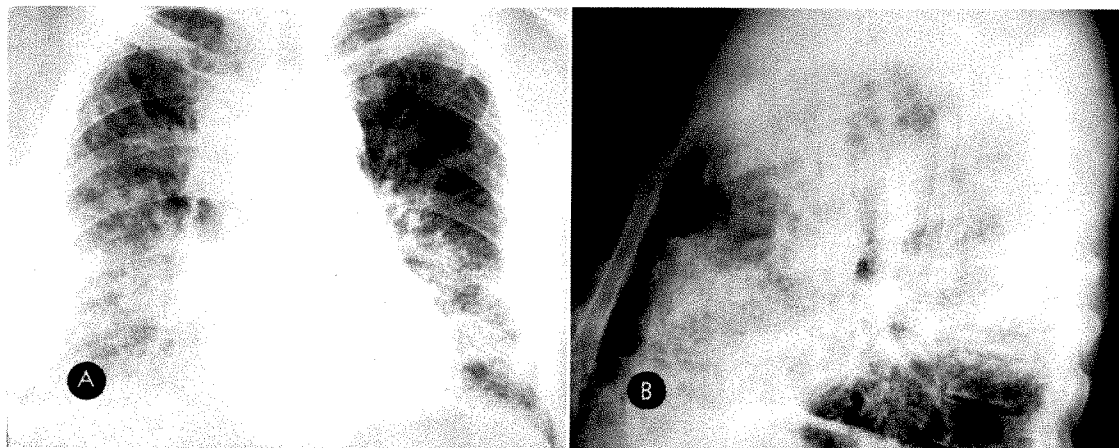


FIG. 3. Case III. Male, aged 48. (*A* and *B*) 11-7-60: Marked fibrosis bilaterally with extensive small cysts in the lower lobes and right middle lobe. Note the right superior mediastinal mass.

tional exposure to dust. The patient was hoarse for 10 years and had had a thyroidectomy in the past for a toxic goiter.

On physical examination, bilateral crackling rales were noted at the bases. Clubbing of the fingers was present. Laboratory studies and cultures were all negative. Chest roentgenograms showed bilateral hilar lymphadenopathy and diffuse pulmonary parenchymal disease. Respiratory function studies demonstrated an alveolar-capillary block with ventilation-perfusion imbalance. Bronchoscopy showed paralysis of the right vocal cord and cytologic studies of the aspirate showed cells with neoplastic changes. The lung biopsy was performed on April 6, 1961 and the cytologic diagnosis was pulmonary muscular hyperplasia. The patient was discharged on prednisone. She has had 2 subsequent admissions with gradually increasing dyspnea.

CASE VI (Fig. 6, *A* and *B*). A 34 year old white female was admitted to another hospital in January of 1961, because of dyspnea on exertion, orthopnea and productive cough. The patient had had rheumatic fever as a child and at the age of 16 she began to develop clubbing of the fingers. In spite of this, she was asymptomatic. She had had 3 normal pregnancies without any cardiorespiratory symptoms. There was no history of hemoptysis or peripheral edema.

Physical examination showed an obese female in no acute distress. There were wheezes in both lung fields and a triple cardiac rhythm with an accentuated pulmonic second sound, but no murmurs. There was marked clubbing of the fingers. Chest roentgenograms showed slight heart enlargement. A bronchogram revealed segmental bronchiectasis in the right lower lobe. An angiocardigram demonstrated

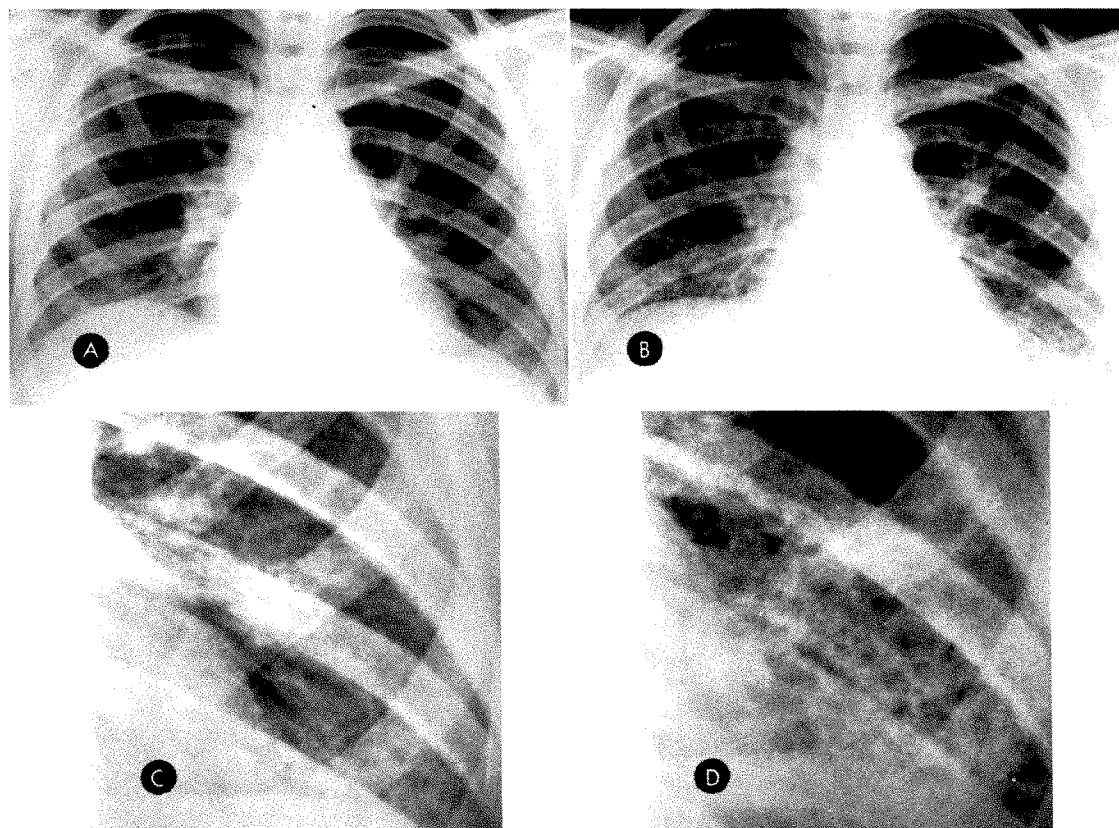


FIG. 4. Case IV. Female, aged 28. (*A*) 11-21-57: Coarse reticular changes in the lung parenchyma. Note the prominence of the right hilar lymph nodes. (*B*) 2-6-64: Progression of changes in 7 years. The fibrotic changes have increased. Note the unequal areas of aeration and microcysts at the base. The hilar lymphadenopathy has also increased. (*C*) 11-21-57: Enlarged view of the left base in *A*. (*D*) 2-6-64: Enlarged view from *B*, showing same area 7 years later. Note the microcysts.

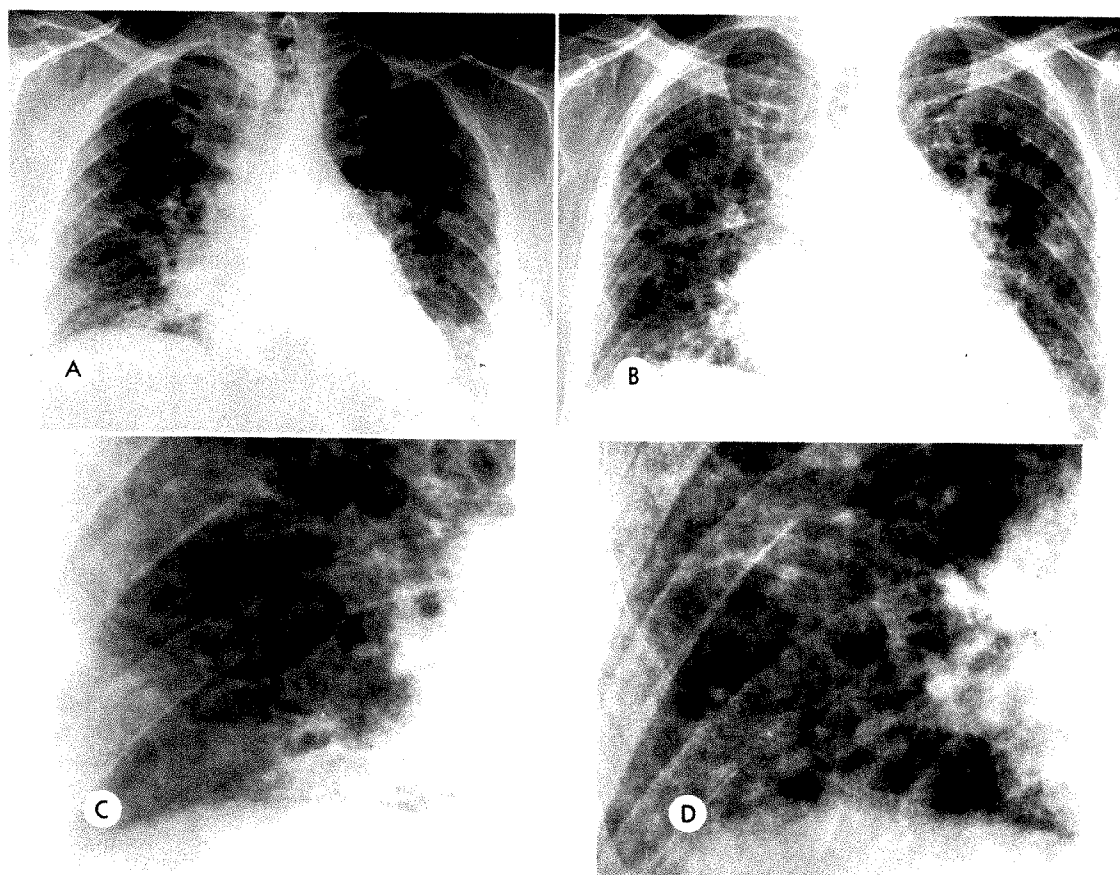


FIG. 5. Case v. Female, aged 54. (A) 2-26-62: Diffuse reticular fibrosis with bilateral hilar lymphadenopathy and prominence of pulmonary artery segment. (B) 9-16-63: Rapid progression in $1\frac{1}{2}$ years with increasing fibrosis and multiple microcysts. (C) 2-26-62: Enlargement of the right base in A. (D) 9-16-63: Enlargement of the right base in B.

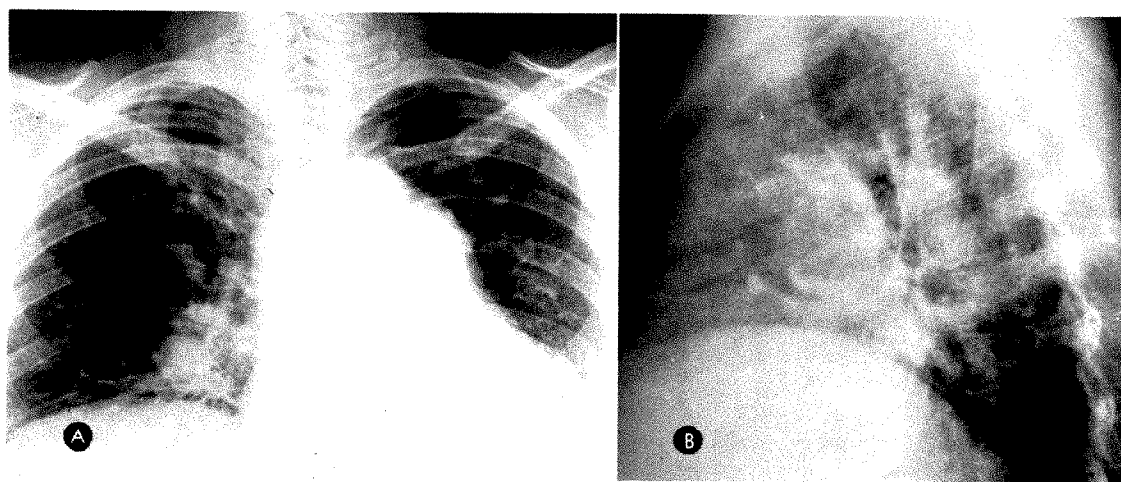


FIG. 6. Case vi. Female, aged 34. (A and B) 10-17-63: Fine fibrotic network, best seen in the left mid-lung field. Note the massive enlargement of the central branches of the pulmonary artery and abrupt narrowing peripherally, characteristic of pulmonary hypertension.

an enlarged right ventricle with dilated pulmonary arteries and major branches associated with marked attenuation of the peripheral vessels. The findings were thought to be consistent with "primary pulmonary hypertension."

Two years later on October 5, 1963, she was admitted to Jefferson Medical College Hospital with pulmonary edema. She responded to oxygen, digitalis and diuretics. A transseptal angiogram was performed to try to delineate the etiology of this patient's cardiac disease. This showed a normal left side of the heart with slight left ventricular hypertrophy. There was right atrial and marked right ventricular enlargement with a greatly dilated

pulmonary artery. The pulmonary artery pressure was elevated to systemic levels (97 mm. Hg).

Two months later the patient was re-admitted with congestive heart failure. After appropriate therapy, an intercostal lung biopsy was done under local anesthesia. The pathologic report was pulmonary muscular hyperplasia. The patient is doing quite poorly with gradually decreasing exercise tolerance.

CASE VII (Fig. 7, *A-F*). A 45 year old white female was admitted to Jefferson Medical College Hospital on May 24, 1961, because of gradual weakness, weight loss and increasing fatigue. She was a known diabetic and had

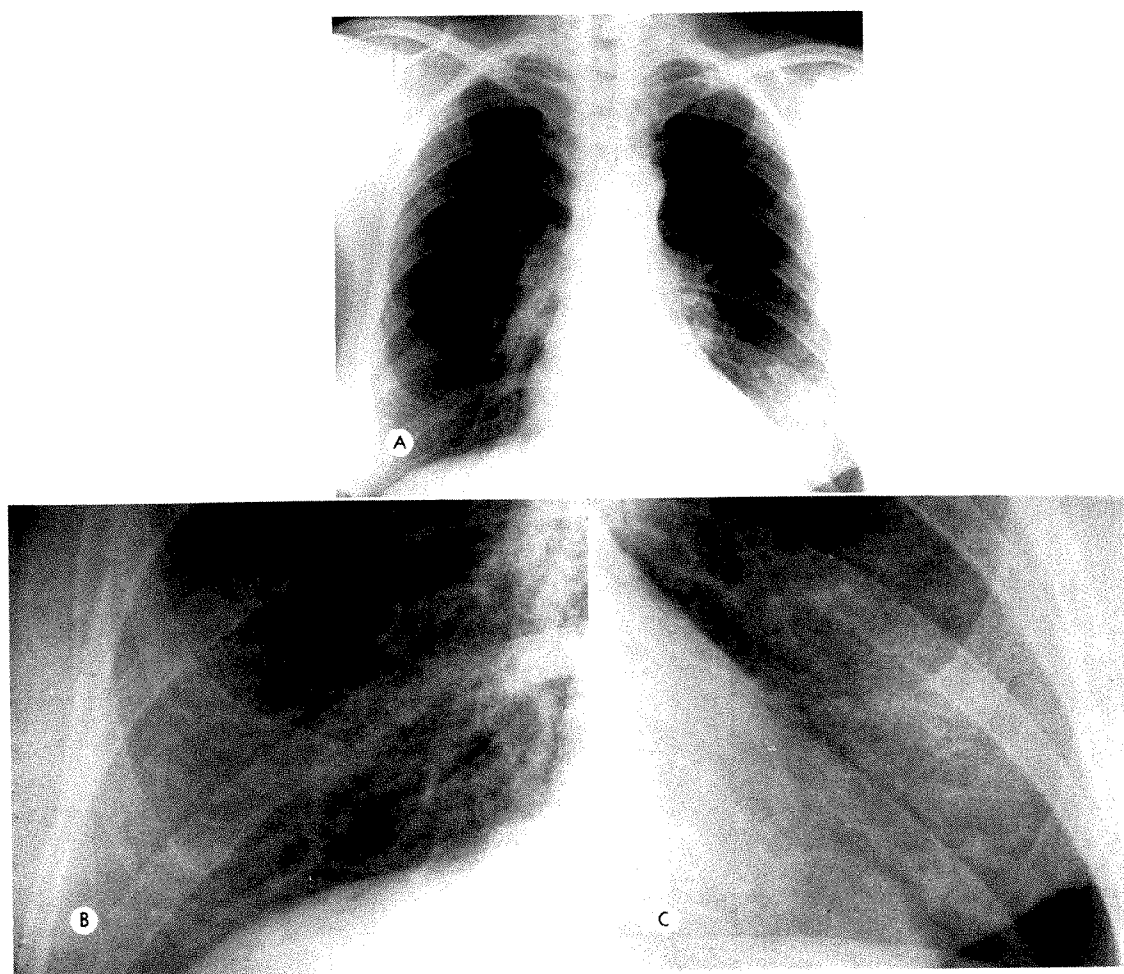


FIG. 7. Case VII. Female, aged 45. (*A-C*) 9-25-61: Posteroanterior views. There is a slight prominence of the hili. The very fine parenchymal changes are best appreciated on the enlarged views. (*B*) Magnified view of right base and (*C*) magnified view of left base. The diffuse reticular pattern has a fine nodular quality in some areas.

gradual progressive clubbing of the fingers for about 15 years. Physical examination revealed depigmentation over the chin and bridge of the nose, thought to be discoid lupus. There were no other positive physical findings. Laboratory tests were within normal limits. Respiratory function studies showed an alveolar capillary block. A lung biopsy was performed which was reported as "very early pulmonary muscular hyperplasia or chronic interstitial pneumonia."

CASE VIII (Fig. 8, *A-D*). A 40 year old Negro female was admitted to Jefferson Medical College Hospital on March 27, 1962 with increasing

dyspnea on exertion and left anterior chest pains.

Five years previously, she had been admitted to another hospital where the diagnosis of sarcoidosis was made. Roentgen examinations of the chest showed paratracheal lymphadenopathy with normal hilar structures and clear parenchymal lung fields. Eye examination revealed uveitis. A cervical lymph node biopsy showed changes consistent with sarcoidosis. Laboratory studies showed some evidence of liver injury. Biopsy of multiple skin lesions was considered "lichen planus" with no evidence of granuloma.

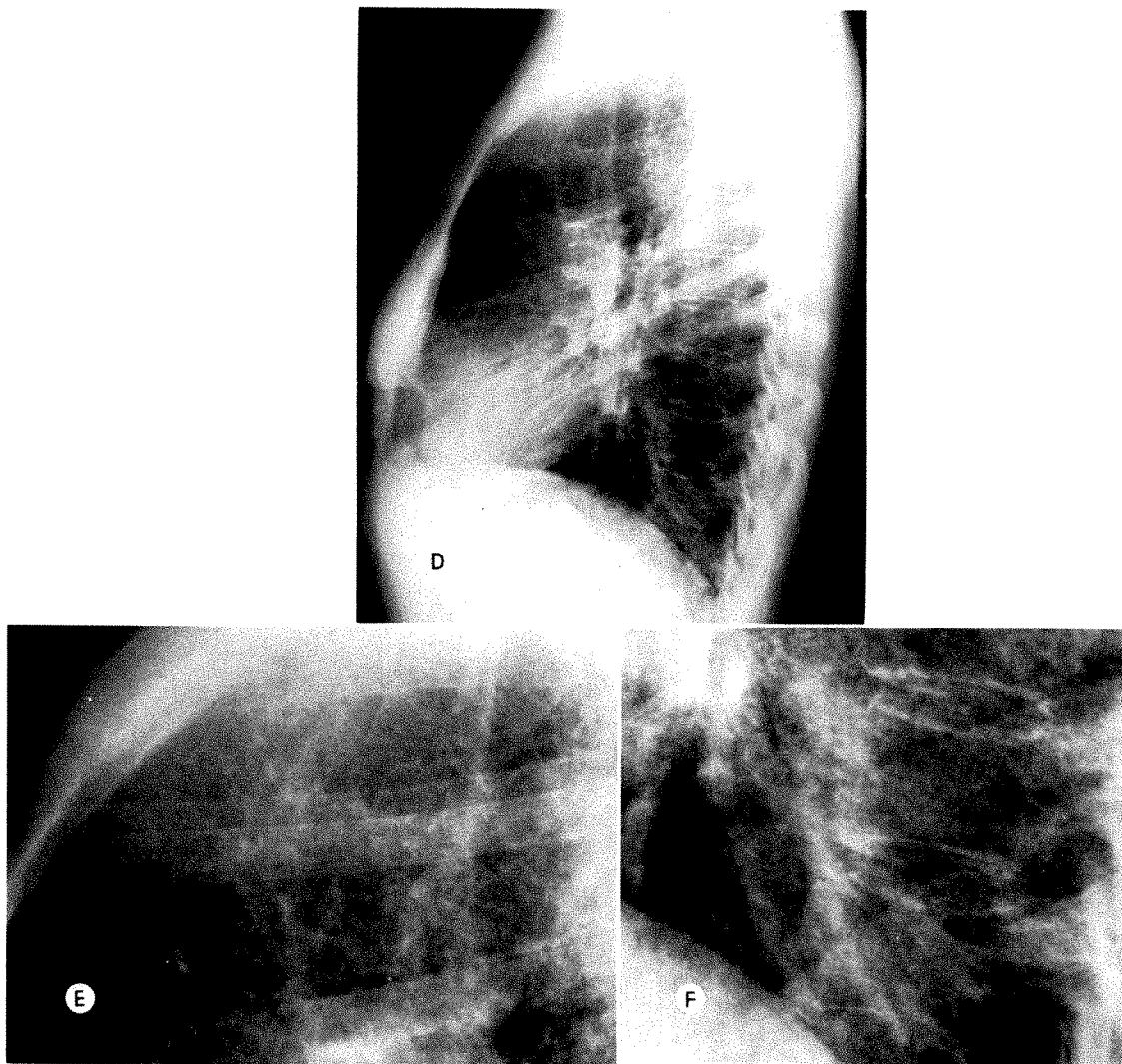


FIG. 7. (*D-F*) Lateral views. (*E* and *F*) Magnified areas of *D*. Note the summation effect of the fine fibrosis often best appreciated in the lateral view because of the increased volume of lung tissue.

Physical examination on admission to Jefferson Medical College Hospital confirmed the presence of the previously described skin lesion and eye changes. Numerous moist rales which did not clear with coughing were present in the chest. The liver was enlarged 2 to 3 finger

breadths below the costal margin. The spleen was not palpable. Laboratory studies including sputum culture and liver function studies were negative. Pulmonary studies showed some obstructive disease and a diffusion block. Tests for histoplasmosis were strongly positive.

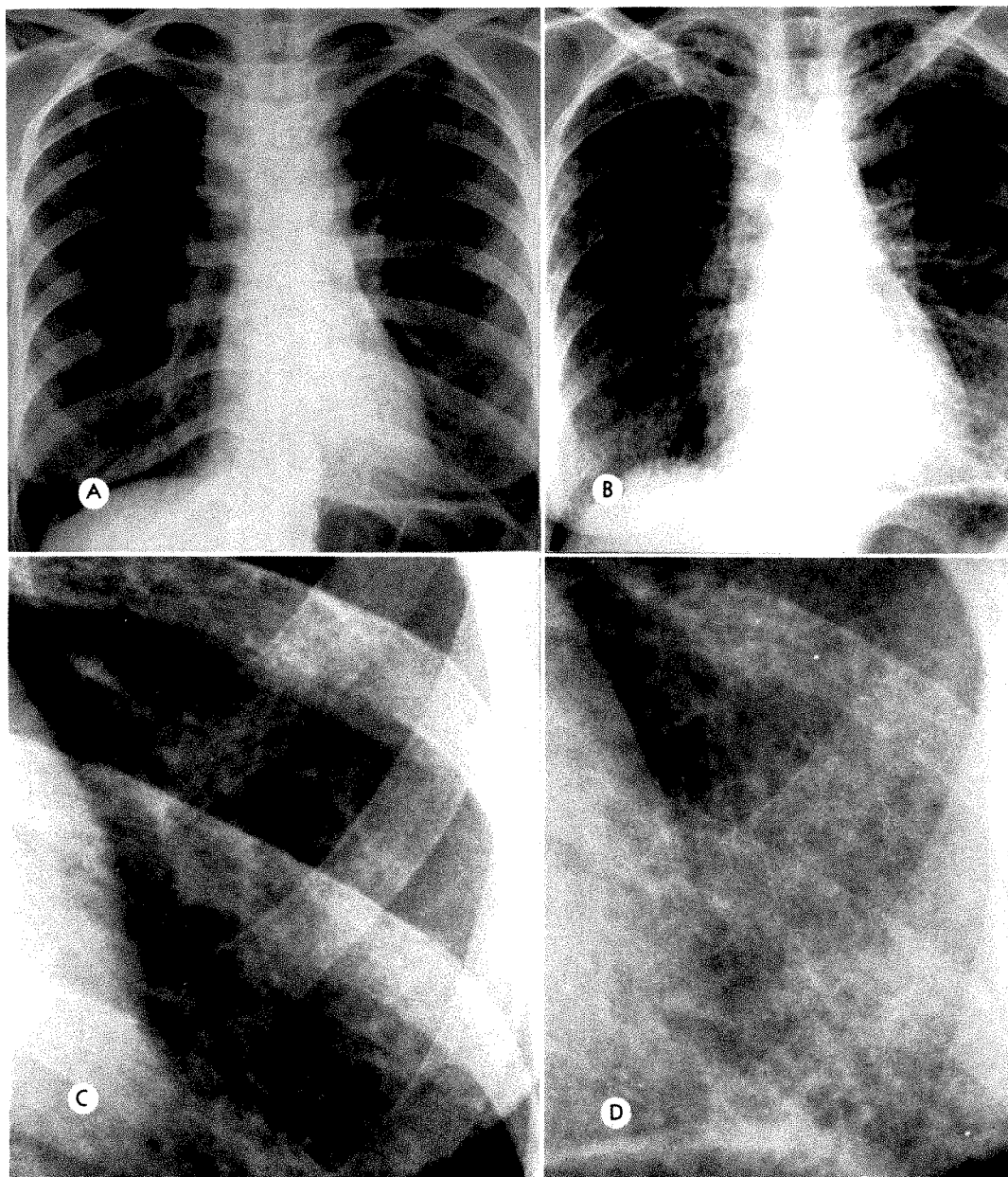


FIG. 8. Case VIII. Female, aged 40. (A) 8-1-55: Paratracheal lymphadenopathy and minimal fibrosis in lung fields. (B) 4-18-63: The lymphadenopathy persists and there has been a marked increase in the all parenchymal lung fibrosis. (C) 8-1-55: Magnified area of the left base in A. (D) 4-18-63: Magnified area of left base in B, showing same area 8 years later. The microcysts are now apparent. Biopsy revealed pulmonary muscular hyperplasia with no evidence of granulomata.

but the serology was only weakly so. Sarcoidosis was still the clinical diagnosis.

In February, 1963, the patient was re-admitted for a lung biopsy because of progressive roentgen evidence of parenchymal lung disease. The histologic diagnosis was pulmonary muscular hyperplasia with no evidence of granulomata. The patient has shown some slight improvement on steroid therapy.

CASE IX (Fig. 9, *A-D*). A 48 year old white male was admitted to the Jefferson Medical College Hospital on June 11, 1962, with a 4 year history of gradual progressive dyspnea. Yearly chest roentgenograms were reported as normal

until 1 month prior to admission when some pulmonary fibrosis was noted. The patient had a dry morning cough and smoked $1\frac{1}{2}$ to 2 packages of cigarettes per day. Recently, he had developed a productive cough with a small amount of yellow sputum. There was a 10 pound weight loss, but no hemoptysis or night sweats. Seventeen years previously, he first began to note clubbing of the fingers.

Physical examination revealed marked clubbing of the fingers and toes. There were sibilant rales in both bases. The second cardiac sound was markedly accentuated in the pulmonic region. Skin tests were negative for tuberculosis and positive for histoplasmosis. Roentgeno-

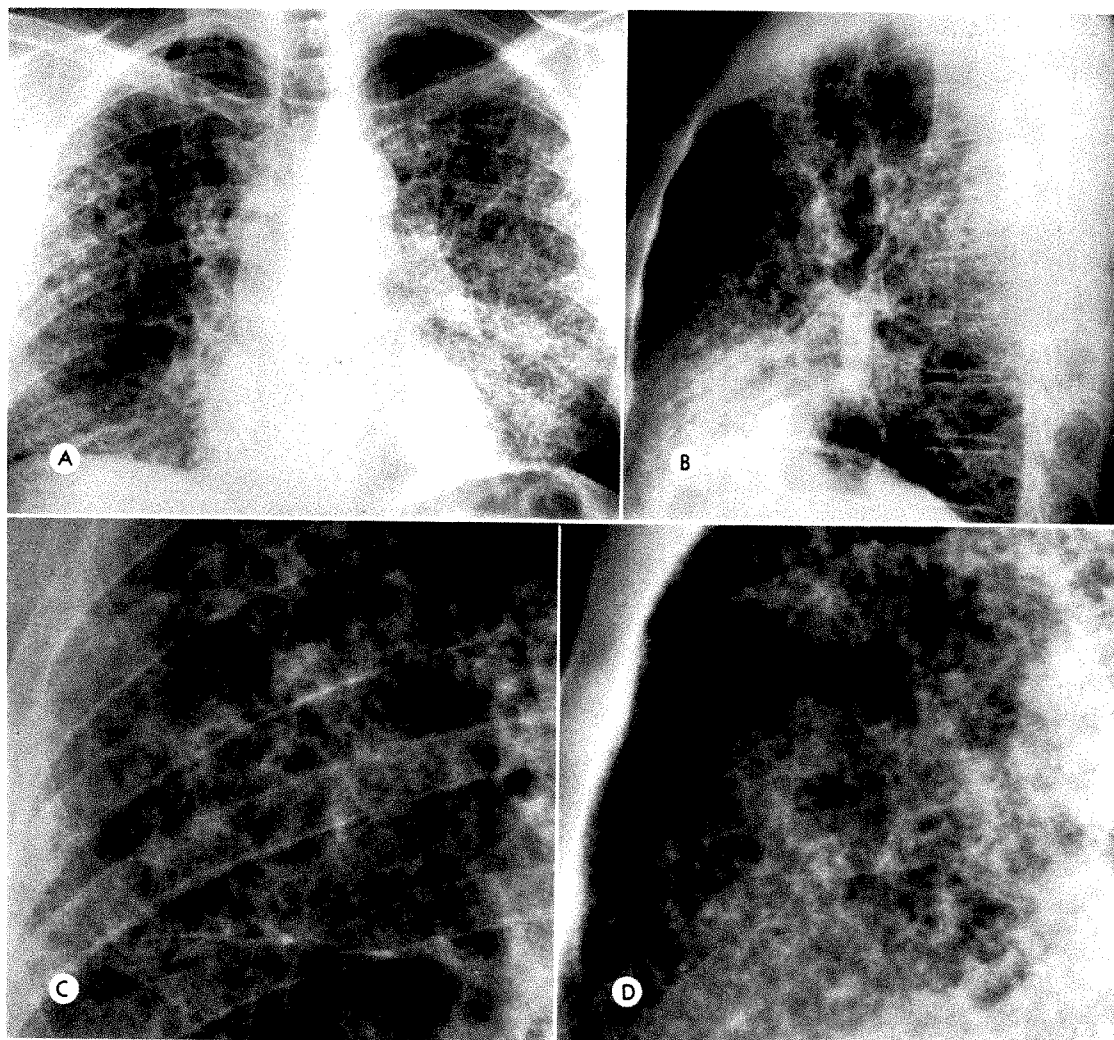


FIG. 9. Case ix. Male, aged 48. (*A-D*) 4-24-63: (*A*) Posteroanterior roentgenogram. Marked lace-like fibrosis with multiple microcysts. (*B*) Lateral roentgenogram. (*C*) Detail of right mid-lung field in *A*. (*D*) Detail of retrosternal space in *B*.

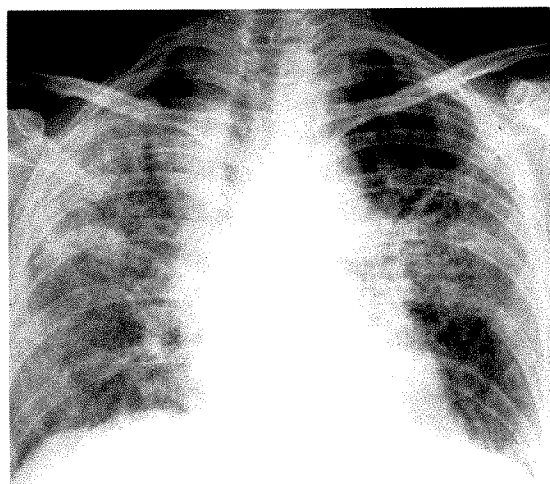


FIG. 10. Case x. Female, aged 58. 1-7-63: Diffuse changes bilaterally with mediastinal widening. Local areas of increased radiodensity were found to be foci of alveolar carcinoma at autopsy.

grams revealed calcific granulomata in the spleen and diffuse interstitial pulmonary fibrosis. Pulmonary function studies demonstrated an alveolar capillary block. A lung biopsy was performed which showed the presence of pulmonary muscular hyperplasia. The patient was discharged on steroid therapy. This was discontinued after the patient developed a peptic ulcer.

CASE X (Fig. 10). A 58 year old white female was admitted to Jefferson Medical College Hospital on September 5, 1962 with an 8 month history of rapidly progressive pulmonary insufficiency. For the last 2 months before admission, the patient had a nonproductive cough. Physical examination was unremarkable. Chest roentgenograms showed chronic inflammatory changes with some pleural reaction at the right base. A bronchogram was made which showed extensive right sided bronchiectasis. Laboratory studies and cultures were all negative. The patient was bronchoscoped and no pathologic findings were present, but the bronchoscopic aspirate showed cells which were suspicious for malignancy.

One month later, the patient was re-admitted with increasing dyspnea on exertion. Physical examination at that time revealed scattered rales bilaterally, especially at the bases. Bronchoscopy and cytology were repeated and were negative. A scalene lymph node biopsy was performed with negative results.

The patient became progressively more dyspneic and cyanotic. She developed minimal clubbing and persistent rales. Sputums were repeatedly negative for routine and acid-fast bacilli. Finally, in December, 1962, a lung biopsy was done which showed pulmonary muscular hyperplasia and areas of squamous metaplasia. The patient did well for 1 month and then suddenly expired on February 11, 1963. At autopsy, focal areas of alveolar cell carcinoma were found.

CASE XI. A 59 year old white male was admitted to Jefferson Medical College Hospital on June 3, 1963, with a 2 year history of dyspnea and fatigue. The patient was referred by a physician because of dyspnea related to exertion which was not improved with digitalis therapy. Chest roentgenograms showed marked pulmonary fibrosis. The patient denied any history of cough, wheezing, hemoptysis, or occupational exposure to dust. A lung biopsy at that time showed interstitial fibrosis of unknown etiology. The patient was discharged on steroid therapy with transient subjective improvement. Gradually, the dyspnea and weakness increased and he was re-admitted to Jefferson on October 18, 1963.

Repeat roentgenographic and laminagraphic examinations at this time showed a significant change, suggestive of development of a mediastinal mass. Physical examination revealed distant breath sounds and fine moist rales at the bases. The liver was enlarged 3 finger breadths below the costal margin. The patient suddenly expired in respiratory insufficiency. Post-mortem examination revealed diffuse pulmonary fibrosis and pulmonary muscular hyperplasia. There were areas of severe squamous metaplasia, but no definite evidence of malignancy.

SUMMARY

Pulmonary muscular hyperplasia is a progressively fatal disease of unknown etiology characterized by the presence of a marked proliferation of smooth muscle elements in the lung and the development of microcysts. Impaired oxygen exchange is the physiologic result of the pathologic changes. The development of carcinoma of the lung has been strikingly high in our series. The radiologist should be aware of

this entity and include it in the differential diagnosis of progressive interstitial fibrosis.

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EXPERIMENTAL APPROACHES TO PULMONARY EMPHYSEMA*

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EMPHYSEMA disables more persons than any other degenerative disease. In fact, it is approaching cancer as a leading cause of death (Fig. 1*A*). This trend is particularly noticeable in California (Fig.

1*B*), no doubt because of the increasing number of senior citizens in this state. Radiologists are understandably concerned with the trend and with investigations of the nature and the causes of emphysema.

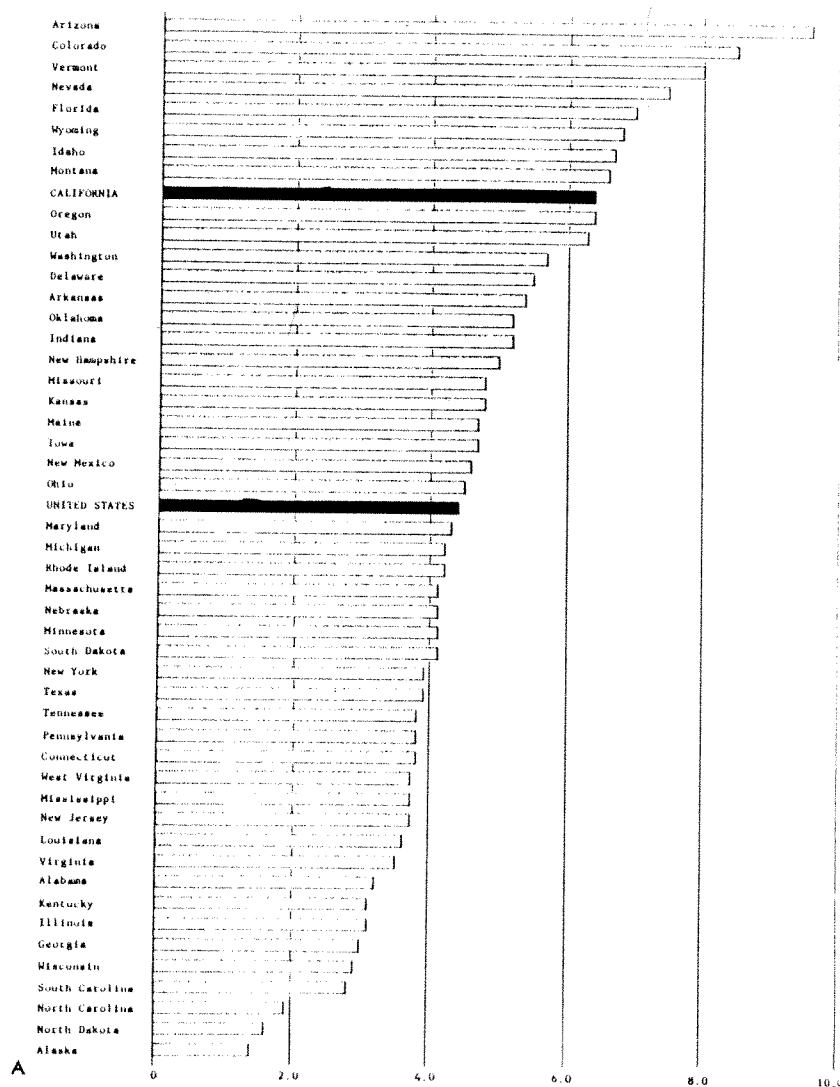
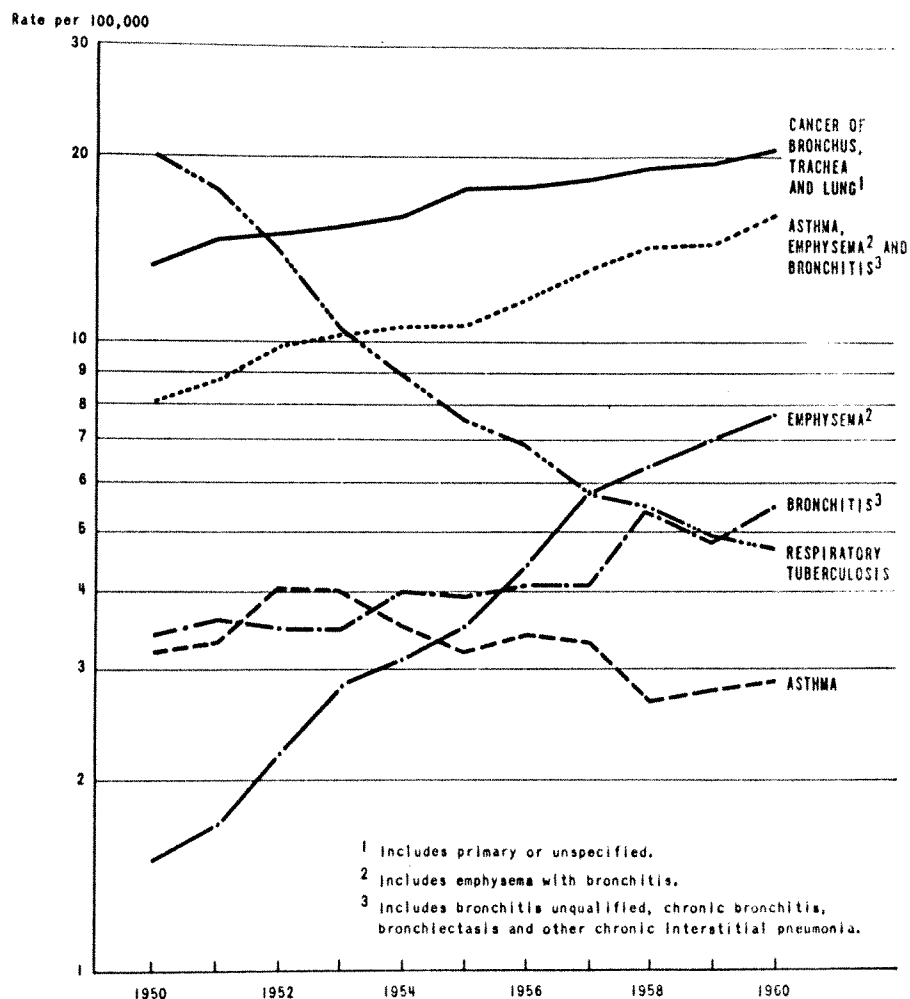


FIG. 1. (*A*) Pulmonary emphysema death rates by State of residence, United States, 1959.

* Presented at the Sixty-fifth Annual Meeting of the American Roentgen Ray Society, Minneapolis, Minnesota, September 2, 1964.



B Source: State of California, Department of Public Health, Death Records.

FIG. 1. (B) Death rates due to selected respiratory diseases in California, 1950-1960.

but they are handicapped by traditionally accepted notions of this disease.

Laennec²⁸ (1800) defined emphysema according to his postmortem observations. His description was so compelling and his pathogenesis so conclusive that his concepts prevail to this day. Therefore, it seemed appropriate when distinguished groups of British and American clinicians agreed on similar definitions.

British CIBA Symposium (1959) definition:

"Emphysema is a condition of the lung characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls."

American Thoracic Society Committee (1961) definition:

"Emphysema is an anatomic alteration of the lung characterized by an abnormal enlargement of air spaces distal to the terminal non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls."

Krahl²⁷ points out as do many pulmonary physiologists that the anatomic definitions concern only a terminal moment in the time relationship of this disease. Their own physiologic studies are justified as ongoing and developmental. They try to identify the disease in its early stages to more certainly define its courses. Their ap-

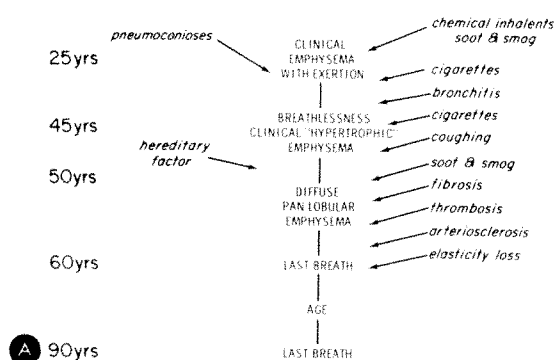


FIG. 2. (A) Time line representing the usual concept of pathogenesis of chronic obstructive respiratory disease.

proach is even more appropriate for roentgenologic investigations even though radiologists are also unable to identify "air spaces distal to the terminal bronchiole."

If one were to draw a time line representing the course of pulmonary emphysema and the factors influencing it, one would probably start in middle age and proceed to the patient's last breath (Fig. 2, A and B). This is the sort of picture which the physiologists and pathologists present.

HYPOTHESIS

There is another end to this spectrum, however, and it may begin before birth. The first causes and the initial pathologic changes probably occur here, in infancy and early childhood. This part of the course of pulmonary emphysema is less recognized and, indeed, many deny its existence. Because it is the early phase and includes the subclinical stage and prevenient factors, this part of the course of the disease is probably the most important to the investigator. Roentgenologic or other very sensitive methods are, therefore, required to study this stage.

Congenital lobar emphysema may lie in that dimly perceived zone of the spectrum. No one knows exactly what causes congenital emphysema and no one knows its exact course. It is known that the large overdistended pockets of lung can rupture, causing mediastinal emphysema, dissection of air along the bronchi, pressure obstruc-

tion of vessels, and often death. One theory of the etiology relates to a deficiency of "surface active material," the absence of which permits progressive overdistention of a few distal segments and associated atelectasis of others. The more widely held theory indicts deficiencies of bronchial cartilage with ensuing flutter valve obstructive effects. Polychondritis of adults may have a similar effect. Tracheomalacia and degenerative bronchial collapse are major factors in the pathogenesis of adult pulmonary emphysema. During life this can be observed roentgenographically, conventionally, tomographically and with cineroentgenography.

We have attempted to reproduce chondromalacic disease in experimental animals by introducing chondrolytic solutions into the segmental bronchial arteries. To date, we have only produced aneurysms and we have become quite familiar with the bronchial arterial anatomy of the dog (Fig. 3, A and B). McLaughlin and others have been more successful in producing emphysema by injecting thorazine, chlorpromazine, or styrene beads into the bronchial arteries of horses.

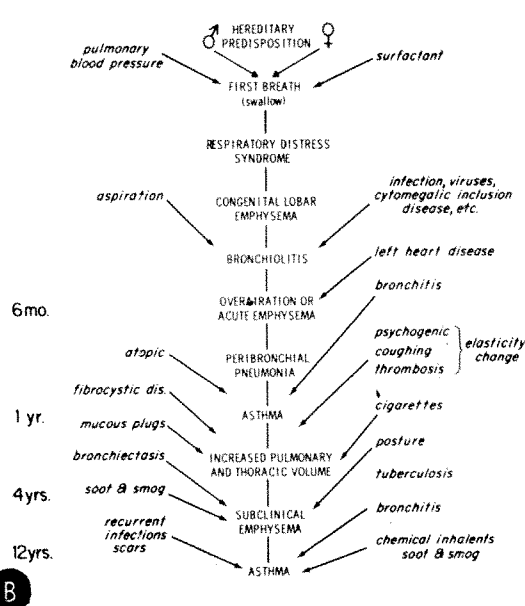


FIG. 2. (B) Time line representing factors and course of patients who later develop overt emphysema.

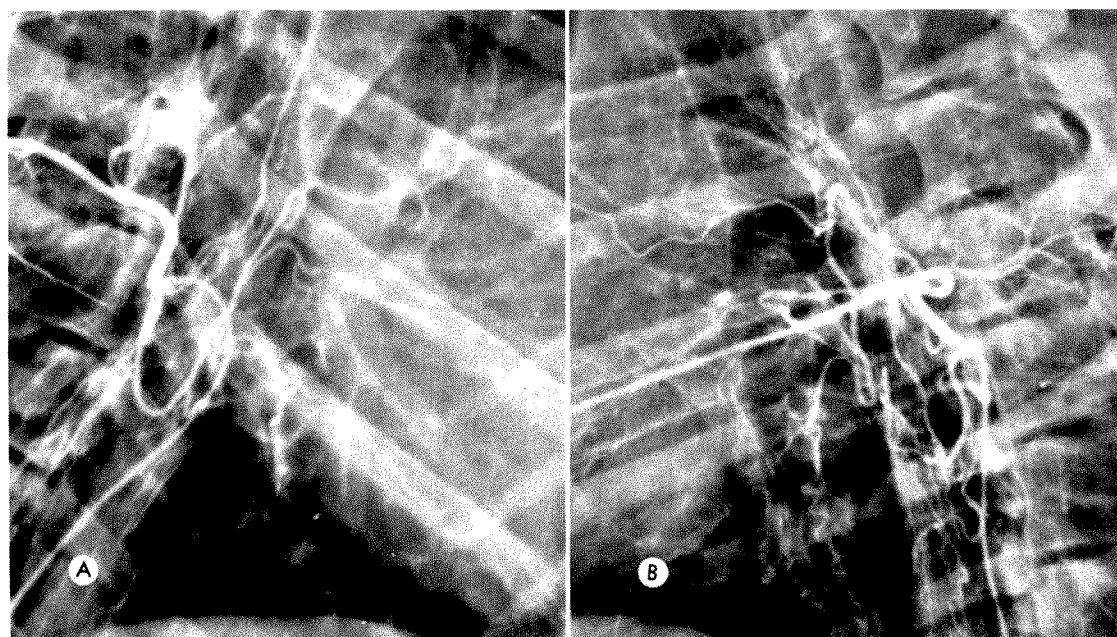


FIG. 3. (A) Selective left oblique bronchial arteriogram of a normal dog. Note ramifications along the bronchi. Unsuccessful attempt to produce chondromalacia. (B) Right oblique bronchial arteriogram, same dog. Esophagus and bronchial walls are partly opacified. Chondrolytic agents injected here did not reach the bronchial cartilages in effective amounts.

CHILDHOOD EMPHYSEMA

Distention of the alveoli and bronchioles can occur in the fetus *in utero* under certain conditions. The resultant thinning of alveolar and bronchial walls and clubbing of septa cannot be called "emphysema" since distention is by a liquid not a gas, but some similarities do exist. There are also similarities to bronchopulmonary sequestration. Surface active lipoproteins in the fetal respiratory fluids potentiate regular distention and tend to prevent atelectasis and segmental or lobar emphysema due to surface tension phenomena (Fig. 4). Premature infants are usually deficient in "surfactant" and often have immediate (hyaline membrane) or delayed (cystic emphysema) respiratory distress. These may be the precursors of later bronchiolitis, asthma, and emphysema. These disorders are ordinarily identified roentgenologically. Breath-holding may be an early expression of the psychosomatic disorder later seen in asthma and emphysema. We are also investigating the psychosomatic and neuro-

logic aspects of chronic obstructive respiratory disease.

Aspiration, allergy and infection embarrass bronchial air flow at an early age, causing so-called pulmonary over-distention or "acute emphysema." Nitrogen

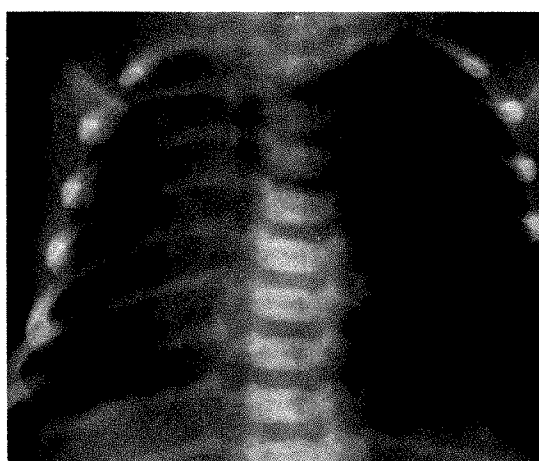


FIG. 4. Newborn infant with congenital "lobar" emphysema which ruptured causing mediastinal emphysema, venous thrombosis and death. Defective cartilages were not identified.

dioxide aerosol also produces emphysema in guinea pigs but not in rats or rabbits.⁵¹ Spasm, peribronchial infiltration and mucosal edema easily compromise the very small lumen of infant bronchioles.⁴⁶ Expira-

tory obstruction is indistinguishable roentgenologically from pulmonary emphysema and frequently becomes irreversible pulmonary emphysema when repeated or prolonged.¹⁸ Chronic changes are more lik

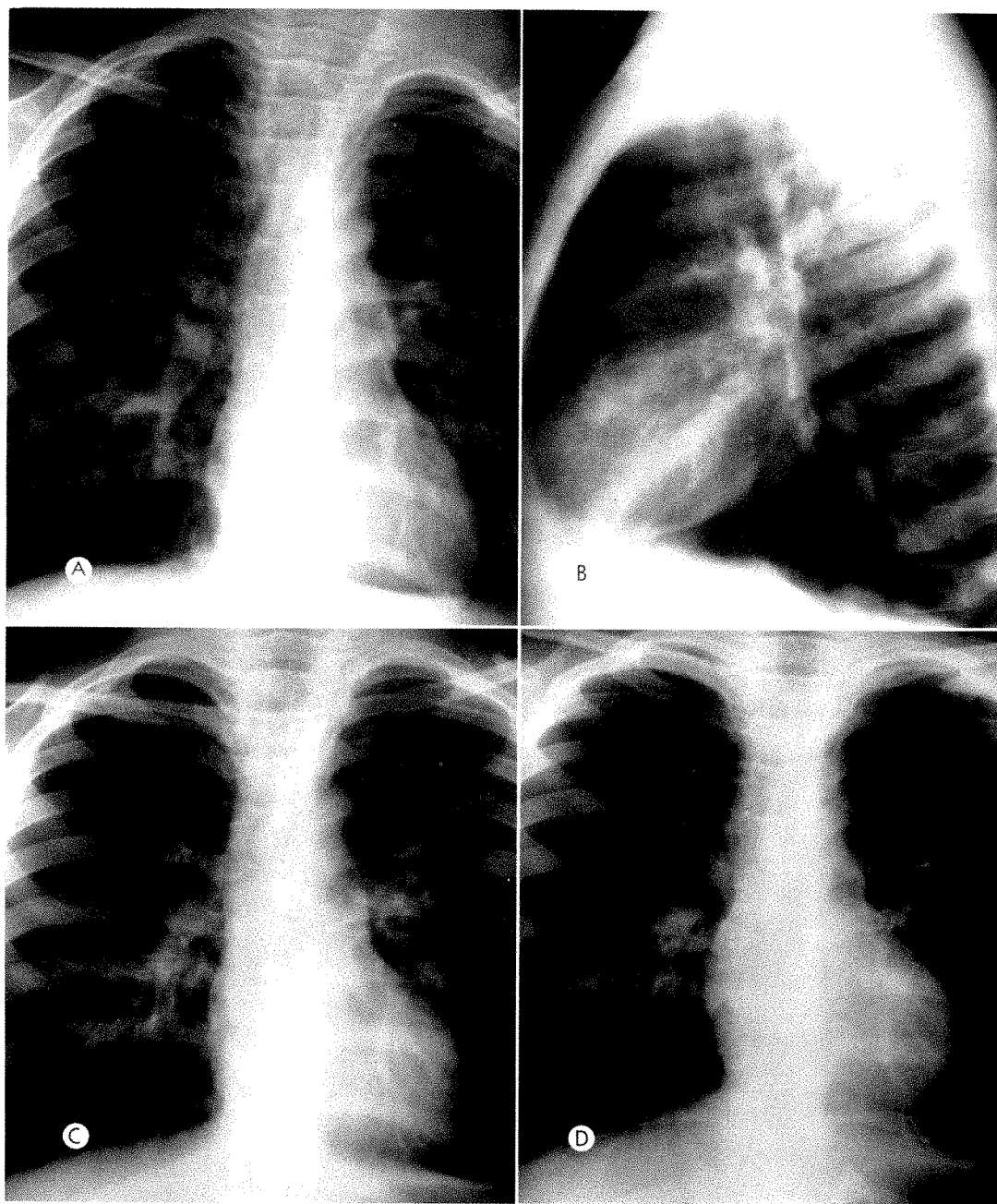


FIG. 5. A.A., 3 year old white male with recurrent asthma and a cold of 3 days' duration. (A) Anteroposterior roentgenogram showing mild pulmonary overaeration. (B) Lateral study. (C and D) Two years later. Exhalation results in very little diaphragmatic motion and in a reduction of heart size and vascular markings.

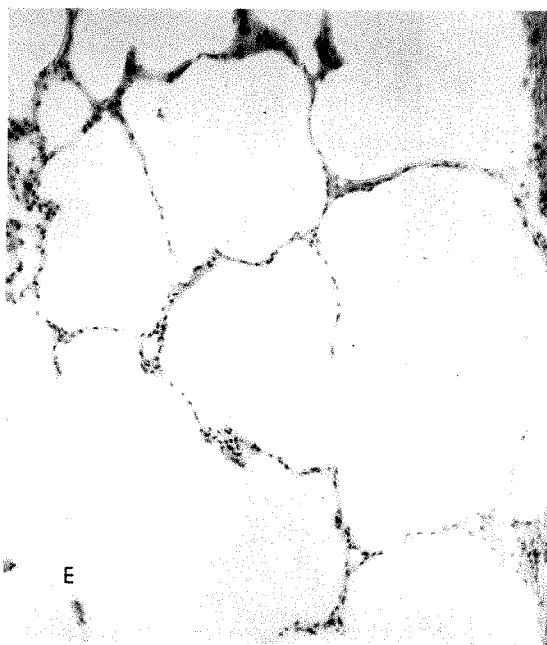


FIG. 5. (E) Patient died during fourth admission in "status asthmaticus." Lung sections characteristic of pulmonary emphysema.

to occur in premature infants or in those who had neonatal respiratory distress syndrome.¹ Respiratory syncytial virus, ECHO virus, and others chronically inhabit many such bronchial trees. Sensitivity to these agents is acquired and a vicious circle is established.

In "asthmatic" children admitted to the hospital repeatedly for recurrent severe respiratory insufficiency, we have often noted a slowly progressive enlargement of

the thorax, an enlargement which is out of proportion to the very slow growth of the children. Progressive, disproportionate thoracic enlargement when "asthma" is in remission would seem to indicate emphysema. Ebert and Pierce,¹³ Rackemann and Edwards,⁴⁰ and others deprecate the significance of such observations, but Farber and Wilson,¹⁶ Messer *et al.*,³⁴ and others support the impression that there is a significant relationship between asthma and emphysema. Children with chronic recurrent asthma who have died have shown histologic evidence of pulmonary emphysema at autopsy (Fig. 5, A-E).

In an attempt to confirm the theory that intermittent allergic episodes can cause pulmonary emphysema, we sensitized a group of guinea pigs to egg albumin. These animals were then exposed to egg albumin vapor twice weekly and developed very satisfactory asthma. Their litter mates were not sensitized or exposed to egg aerosol but were handled similarly, put into breathing chambers similarly and both groups were studied histologically at the end of 7 months (Fig. 9, A-F). Pulmonary emphysema developed in the sensitized guinea pigs but not in the controls (Table I).

All of the animals sensitized and exposed to egg albumin aerosol for 7 months had pulmonary emphysema at autopsy. They and some controls had signs of previous and present pulmonary infections.

TABLE I
INDUCED EMPHYSEMA IN GUINEA PIGS

	No.	Course	Died	Postmortem Lung Findings
Controls	1	poor condition	D.O.A.	pneumonia
	1	poor condition	day 3	hemorrhagic pneumonia
	1	ill on day 10	day 14	liver abscess
	6	good/sacrificed	7 mo.	occasional old healed scars and interstitial fibrosis
Sensitized	7	severe asthma sensitization, 10th day	sacrificed, 7 mo.	emphysema with variation in amounts of inflammatory changes
	3	severe asthma sensitization, 10th day	sacrificed, 7 mo.	bronchiolectasia, emphysema and marked inflammatory changes

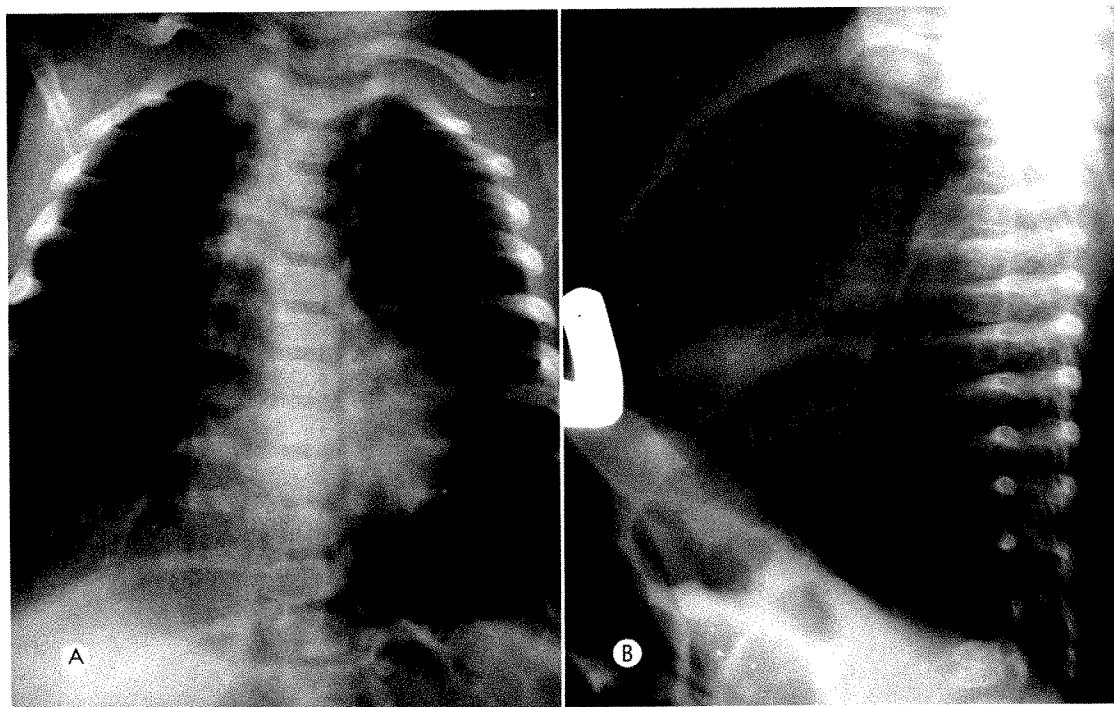


FIG. 6. B.H., a 6 week old white female, was admitted for heart studies with cyanosis, weakness, and failure to thrive. Heart catheterization showed some increase in right-sided pressure but otherwise was normal. Oxygen, penicillin, streptomycin and digitalis therapy gave almost complete remission. (*A* and *B*) Roentgenograms show "snubbed off" arteries, high sternum, low diaphragm, collapse and consolidation with adjacent overaeration.

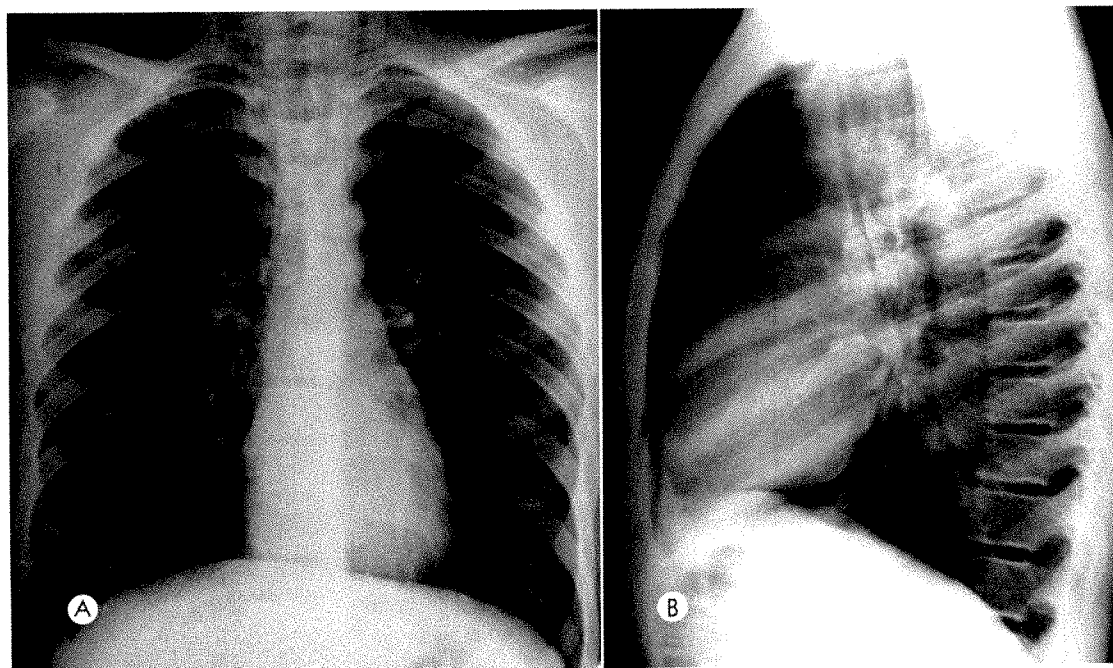


FIG. 7. M.L., aged 12 years, had "asthma" "all his life." (*A* and *B*) Roentgenograms show pneumothorax and mediastinal emphysema, probably from a ruptured bulla.

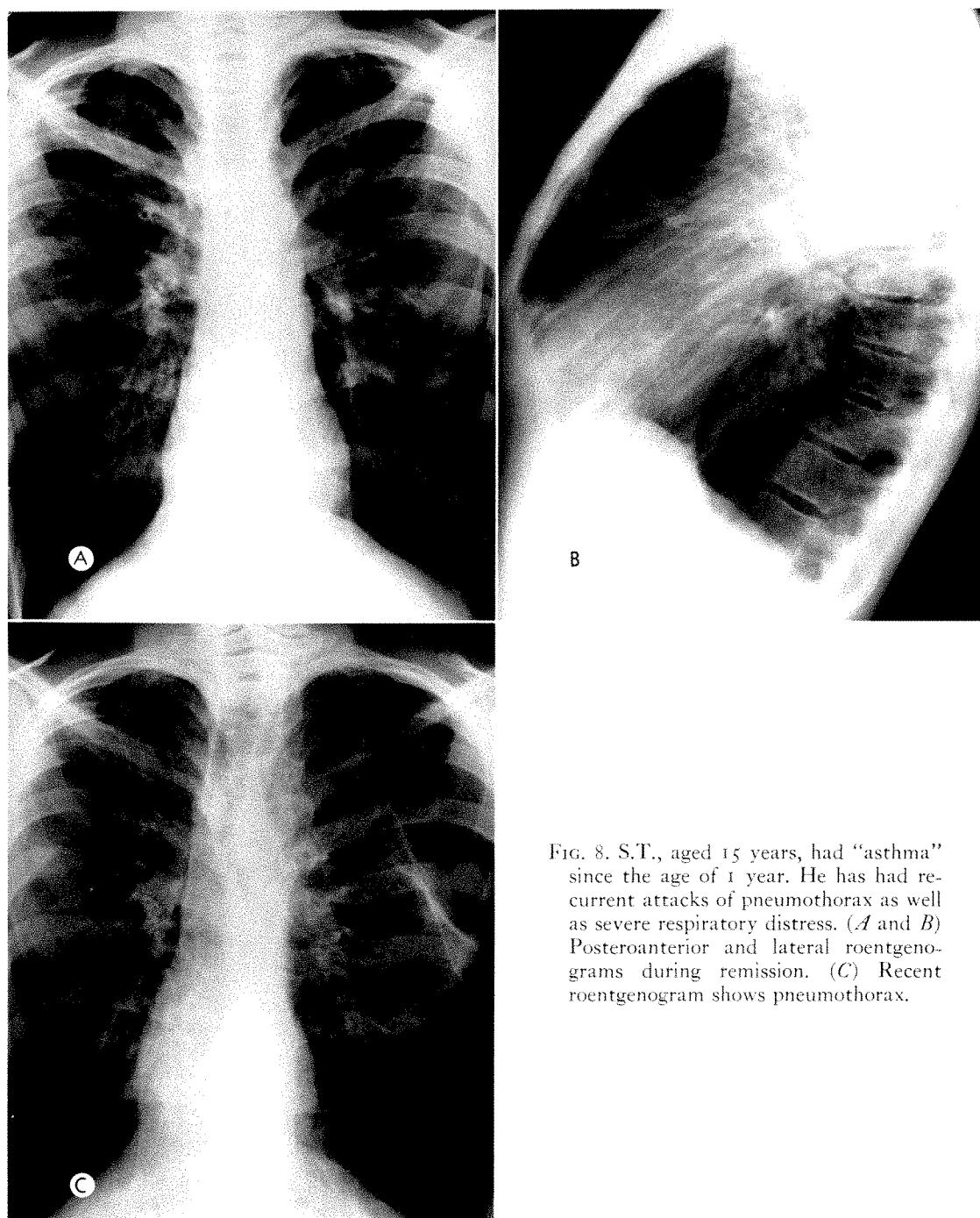


FIG. 8. S.T., aged 15 years, had "asthma" since the age of 1 year. He has had recurrent attacks of pneumothorax as well as severe respiratory distress. (A and B) Posteroanterior and lateral roentgenograms during remission. (C) Recent roentgenogram shows pneumothorax.

It has been said that all that wheezes is not asthma. Often patients with cystic fibrosis present progressive asthmatic changes with later development of severe pulmonary emphysema. These children with cystic fibrosis are good subjects for

studying developing emphysema. Right heart catheterization usually shows a mild increase in blood pressure and small peripheral left to right shunts (Fig. 6, A and B). A wedge injection usually shows a good capillary blush with some straightening and

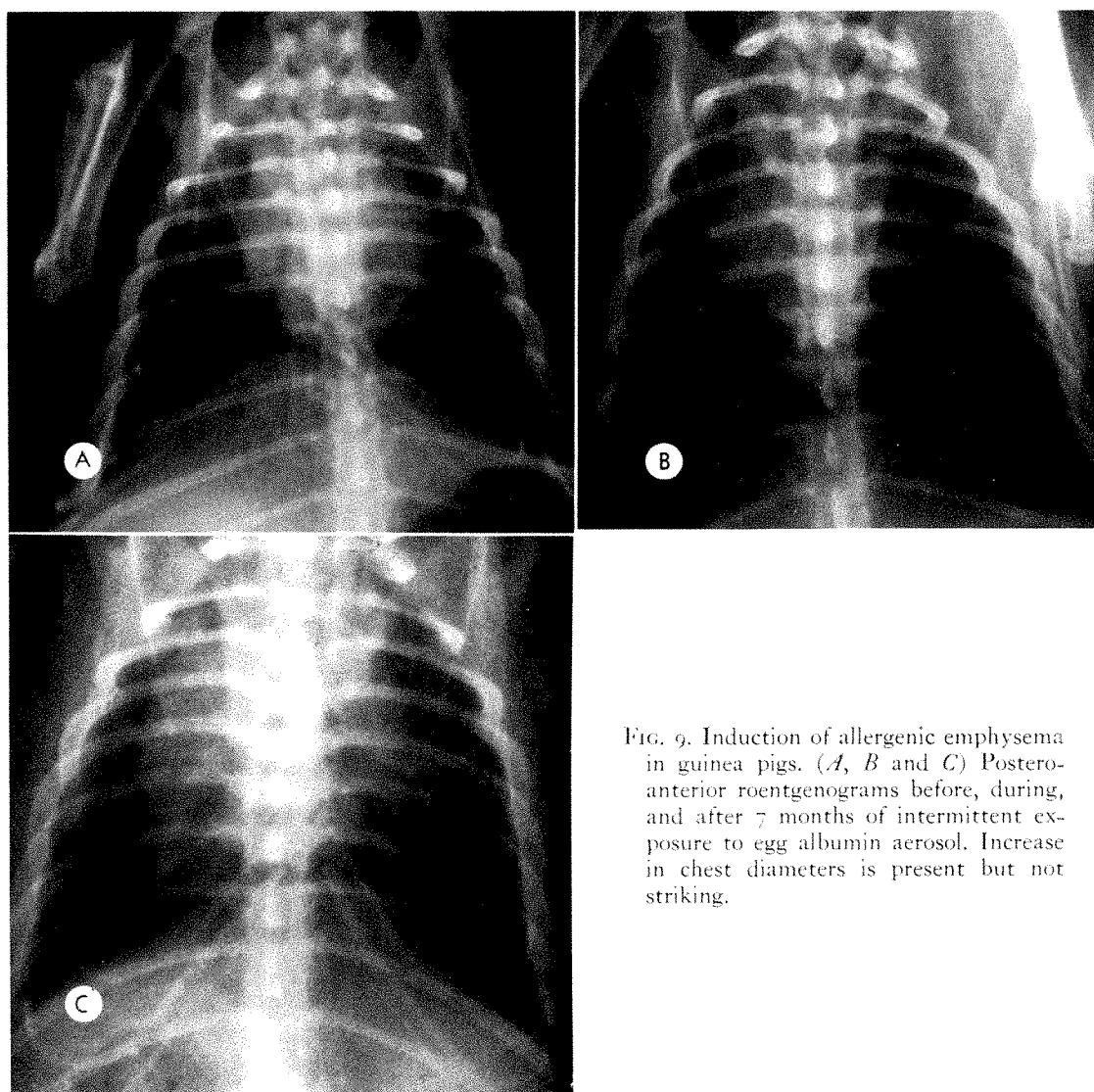


FIG. 9. Induction of allergic emphysema in guinea pigs. (*A*, *B* and *C*) Postero-anterior roentgenograms before, during, and after 7 months of intermittent exposure to egg albumin aerosol. Increase in chest diameters is present but not striking.

squaring of arterial branches as is seen in other types of hypertension. Large shunts have not been seen. Bronchial arteries are large and tortuous and have an increase in their pulmonary arterial anastomoses. Bronchial artery disease has been mentioned as a major cause of pulmonary emphysema, but we are not certain whether the changes we see are causes or effects (Fig. 10 through 12, inclusive).

Congenital absence or severe coarctation of the pulmonary artery also is associated with emphysematous changes in the lung and with pulmonary hypertension.³⁶

Obstruction of the pulmonary arterial circulation produces emphysema in rabbits (Fig. 13, *A* and *B*; and 14).⁴³ Experimental pulmonary arterial coarctation was produced by loosely ligating the pulmonary arteries of puppies and allowing them to grow up around the ligatures.¹⁵ Pulmonary hypertension developed; however, emphysematous changes were not found. Perhaps the animals should have been observed for a longer period. This experiment has been confirmed in calves and lambs.⁴⁷

In using experimental animals for studies on pulmonary function or emphysema,

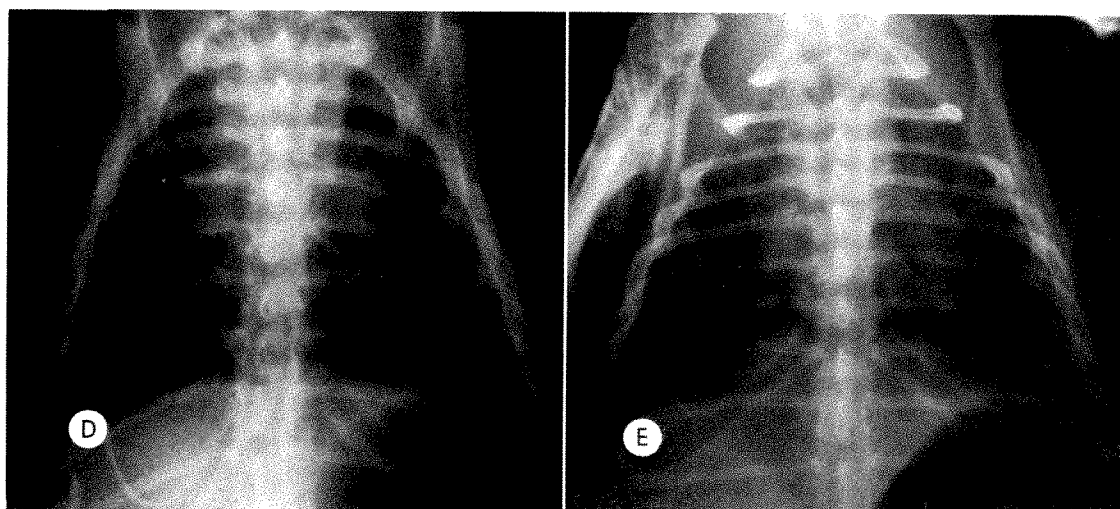


FIG. 9. (D and E) Normal controls similarly handled.

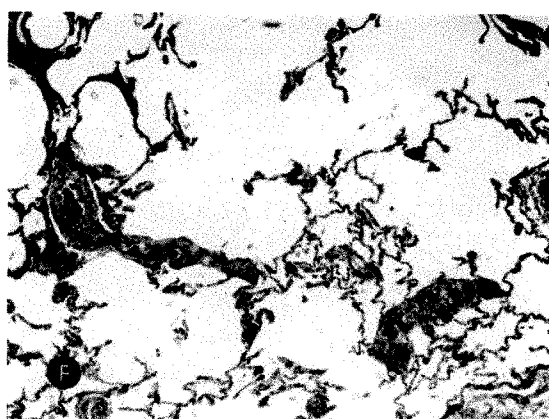


FIG. 9. (F) Lung section of a sensitized guinea pig showing alveolar stretching, thinning of walls, clubbing of septa and other signs of emphysema.

one must remember that the anatomy of the lung is quite different for different species and that, for instance, in the anatomy of the bronchial arteries, the horse most closely approximates man.³³ The horse also happens to be the only animal other than man that spontaneously develops pulmonary emphysema (Table II).

ADULT EMPHYSEMA

Roentgenologic procedures have been used more frequently in investigating the commoner adult pulmonary emphysema. Barden as well as Laws and Heard,³⁹ and Mori and his associates³⁵ have added to the general knowledge of chronic obstructive

TABLE II
ANATOMIC LUNG TYPES

	Cow, Sheep, Pig	Monkey, Dog, Cat	Horse, Man
Lobulation	extreme	absent	imperfect
Pleura	thick	thin	thick
Pleural Blood	bronchial artery	pulmonary artery	bronchial artery
Pulmonary Vein	close to bronchus	independent course	close to bronchus periph-
			erally, apart at hilus
Terminal Bronchial Artery	distal airway	distal airway	distal airway and alveoli
Terminal Bronchioles	present	absent	present
Respiratory Bronchioles	rare to absent	well developed	poorly developed
Bronchial Pulmonary			
Arterial Shunts	present	absent	present

respiratory disease by their roentgenologic studies. Spirometry in conjunction with roentgenography (Barden) should be helpful in evaluating the physiologic correlates of roentgenologic emphysema. Mori *et al.*³⁵ found a high correlation between physiologic emphysema and certain roentgen signs as used by his radiologic colleagues in Florida. His observations are worth reiterating (Table III).

In comparing roentgenologic and au-

topsy findings, Laws and Heard³⁰ found that an abrupt change in the caliber of the pulmonary arteries on roentgenograms was the most common sign. The other signs listed in Table III were also helpful, but narrowing of the 3rd to the 5th branches of the pulmonary artery was found most consistently. Tomographic studies increase the reliability of this sign and also show bullae more clearly.

Volumetric chest measurements on

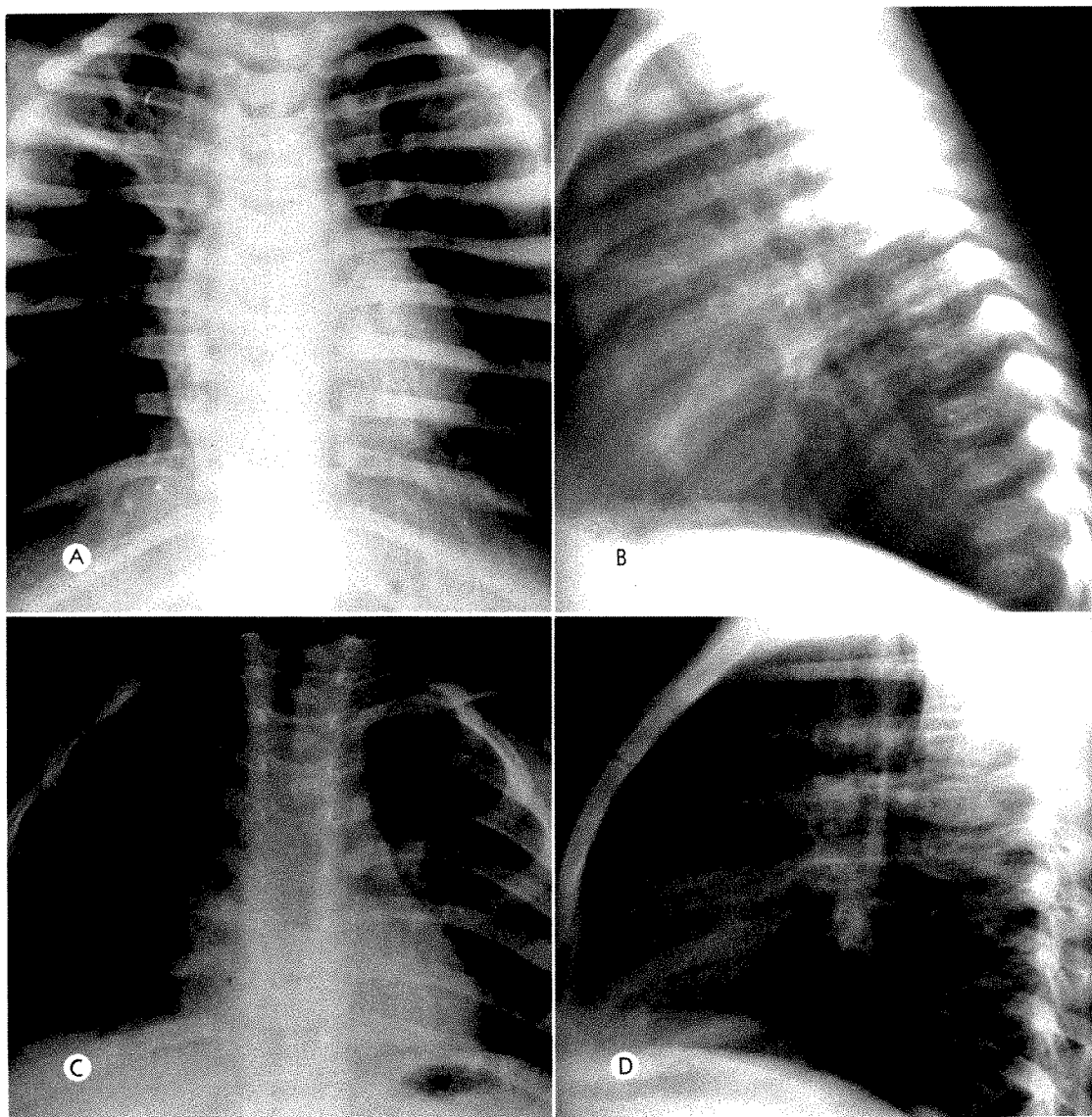


FIG. 10. Fibrocystic emphysema. Four year old white female with dyspnea, retraction of ribs and other signs of respiratory disease. (A and B) Localized right upper lobe consolidation. Diagnosed and treated for "bronchiolitis." (C and D) Patient had intermittent "asthma" and failed to respond to treatment.

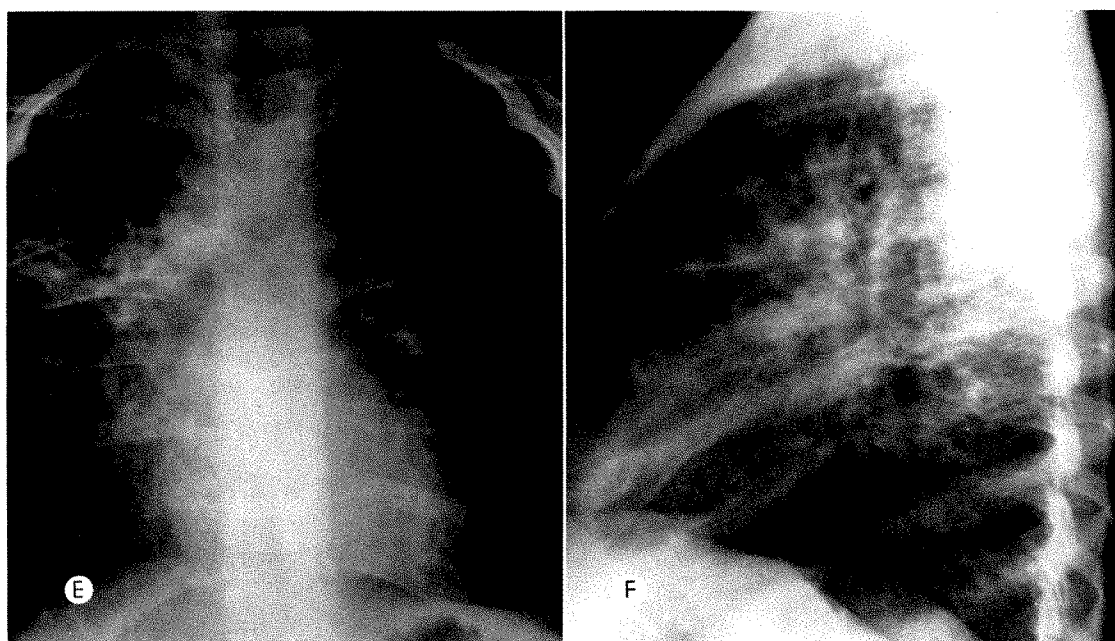


FIG. 10. (E and F) At 6 years of age obvious pulmonary fibrocystic disease with emphysema is demonstrated.

roentgenograms are helpful and correspond well to physiologic lung volume if Barnhard and co-workers⁶ method is used. We are employing this technique along with "thoracic index" measurements to assay

the performance potential of athletes. Some interesting associations between roentgenologic chest configuration and athletic performance are being noted.

Goldenthal *et al.*¹⁹ studied emphysema-

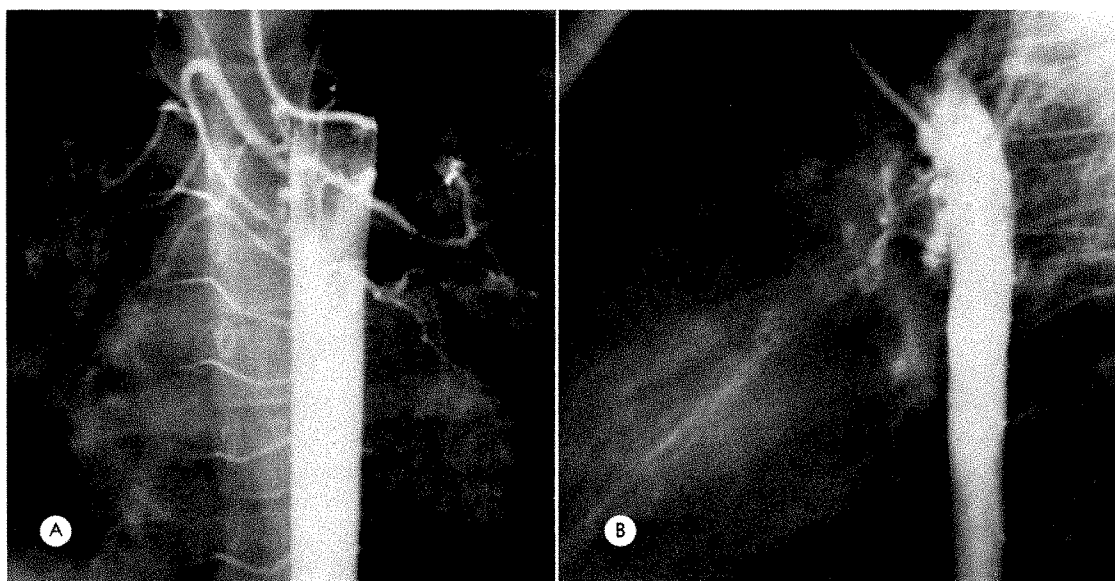


FIG. 11. Bronchial arteries in fibrocystic emphysema in a child. (A) Anteroposterior arteriogram shows the enlarged, tortuous bronchial arteries. Normally, they are the size of the intercostals. (B) Lateral roentgenogram shows rich pleural plexuses extending along the long fissures.

tous patients with roentgenkymography. The curving shadows of diaphragmatic motion during maximum forced expiration corresponded well with physiologic spirometric curves. Lasser²⁹ modified this method for the investigation of specific respiratory impairments. In his report, dia-

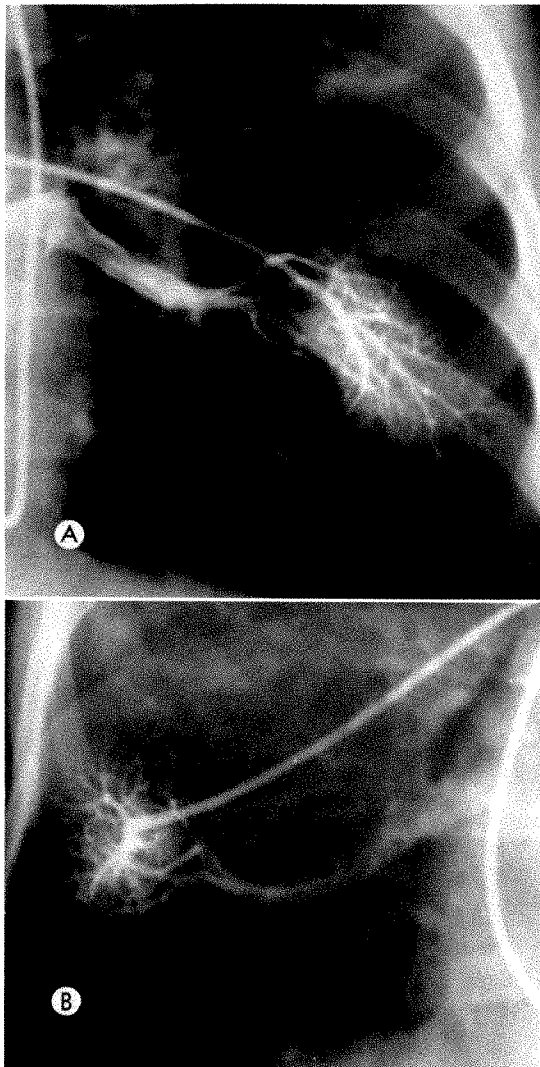


FIG. 12. Pulmonary arteries in fibrocystic emphysema. (A) Pulmonary arterial wedge injection shows normal looping capillary circulation. Right to left shunt here must be small if present. (B) Wedge injection in a child also with fibrocystic emphysema but with a higher pulmonary artery pressure. Note the sharp, almost right angle arterial branching and the shunts to the pulmonary vein, bypassing many of the capillaries.

TABLE III
PHYSIOLOGIC AND ROENTGENOLOGIC
SIGNS OF PULMONARY EMPHYSEMA

Roentgenologic Sign	Physiologic Emphysema Correlation Coefficient	Agreement among Radiologists
Serration of Diaphragm	.5321	90%
Bullae	.5309	90%
Excursion of Diaphragm	.5236	81%
Prominence of Pulmonary Artery	.4702	85%
Sternal Prominence	.4467	87%
Retrosternal Space	.4452	85%
Position of Diaphragm	.4265	89%
Vascularity of Lungs	.4233	87%
Anteroposterior Diameter of Chest	.4211	89%
Translucency of Lower Lung	.4159	85%

phragm and rib motions are well shown shifts in blood or other intrathoracic fluids are not recorded. Oderr³⁸ estimates pulmonary insufficiency by fluorodensitometry.

Pathologists have noted the predilection of emphysematous lesions in the apical portions of the lungs (Fig. 14). Hydrostatic effects should be included among many factors which are considered in production of these lesions. In chest roentgenography hydrostatic effects are observed ordinarily as an increase in density at the dependent bases of the lower lobes (Fig. 15, A-F). This density is accentuated by exhalation. If the subject is inverted (head down position), this phenomenon is noted in the upper lobes, again most prominently when the subject exhales.⁴⁴ Similarly, in the decubitus position, the dependent portion exhales less efficiently than does the upper. Evidently hydrostatic pressure assists exhalation. The fruit jar model shows how this works (Fig. 16, A, B and C). It also shows that the upper portion of the system does not change air as well as the lower. In the absence of surfactant, there would be a

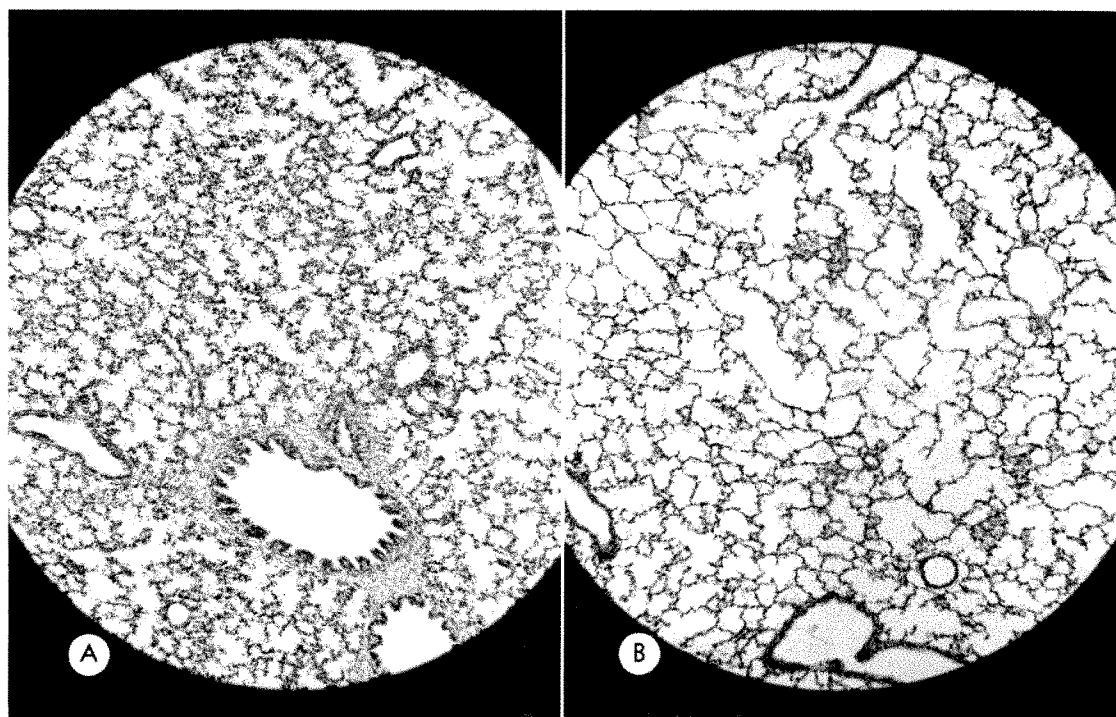
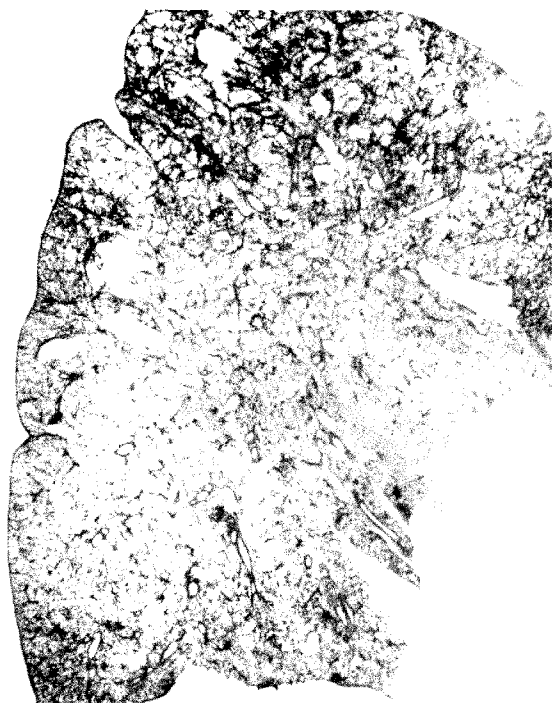


FIG. 13. Obstructive fetal lung changes. (A) Normal fetal rabbit lung. (B) Fetal rabbit lung after *in utero* bronchial ligation. Alveolar distention, septal clubbing and occasional areas of coalescence resemble the changes of pulmonary emphysema.



ency to overfill the larger upper air sac at the expense of the smaller, possibly contributing to the emphysema of the upper segments. Decreased air exchange also leads to reduction in blood flow to the part, in which ischemia may also contribute to emphysema.

DISCUSSION

It appears that no single factor or agent can fulfill Koch's postulates for pulmonary emphysema. Many factors undoubtedly contribute to chronic obstructive respiratory disease and, as we have shown here, some of them can produce the disease but



FIG. 14. Whole lung section showing characteristic location of emphysematous lesions. Blebs and bullae are noted most prominently in the superior portions of the lung.

are not in effect in all cases. It also appears that the commonly used physiologic diagnostic methods and, of course, the histologic diagnostic methods do not provide a diagnosis until late in the course of the disease. Symptoms of chronic obstructive respiratory disease do not appear until over one-half of the pulmonary tissue has been destroyed. The onset of symptoms is, therefore, related to metabolic and physical activity for a given amount of lung destruction. Elastic tissue proliferation and degeneration are associated with pulmonary activity and destruction. Centrilobular emphysema is found in nearly all aged men at autopsy. Although there are undoubtedly some familial and many environmental factors, time alone may be a major one. Decreased metabolic and physical activity of old age masks "senescent" emphysema.

Therefore, it remains to a nondestructive system, more sensitive than physiologic testing, to explore the earliest stages of

pulmonary emphysema. Radiology provides such systems. They must be used with well designed experiments in the testing of old, new and as yet unconceived hypotheses.

We have as yet been unsuccessful in the production of chondromalacia in experimental animals but we have observed it clinically in patients who develop chronic obstructive respiratory disease.

We have observed recurrent asthma leading into pulmonary emphysema and have reproduced the disease by inducing recurrent chronic asthma in guinea pigs. True, there were associated inflammatory changes in the experimental animals at autopsy—but such changes are also commonly seen in asthmatics.

We have observed cystic emphysematous changes in patients with absent or atrophic pulmonary arteries. Those with pulmonary artery "coarctation" had pulmonary hypertension. We were able to reproduce the pulmonary hypertension in

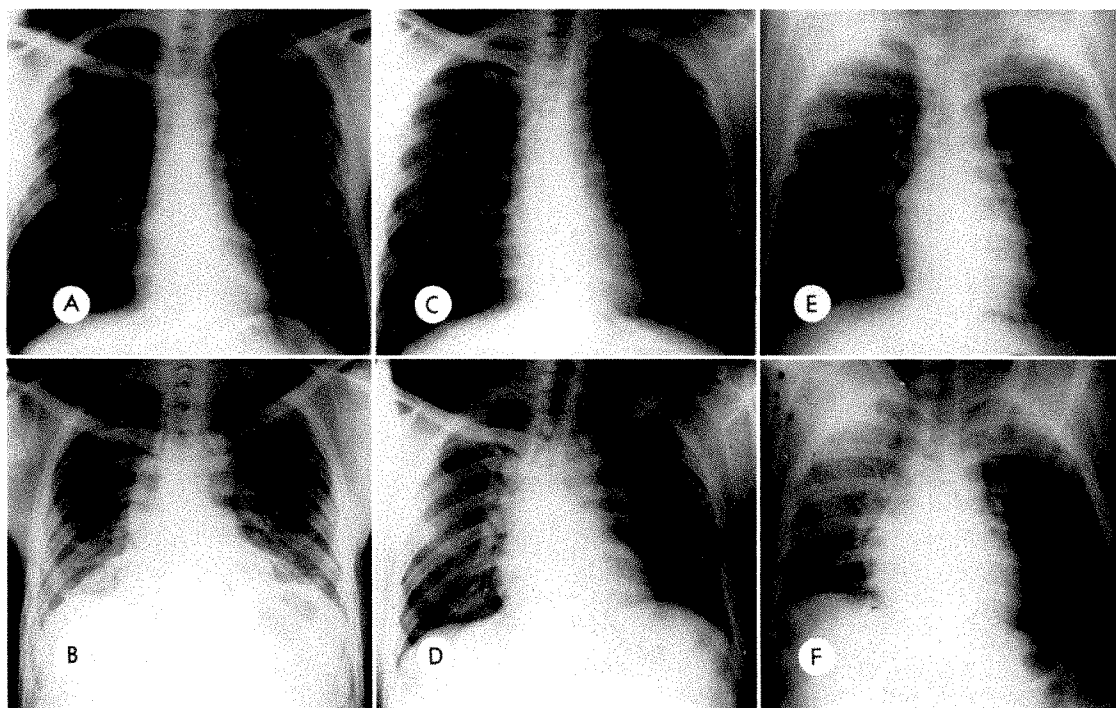


FIG. 15. Studies showing fluid shift in lung due to gravity in the human. (A) Inspiration upright; (B) expiration upright; (C) inspiration upside down; (D) expiration upside down; (E) inspiration decubitus; (F) expiration decubitus. Note that the effective respiration is in the most dependent regions while the upper regions are quiescent.

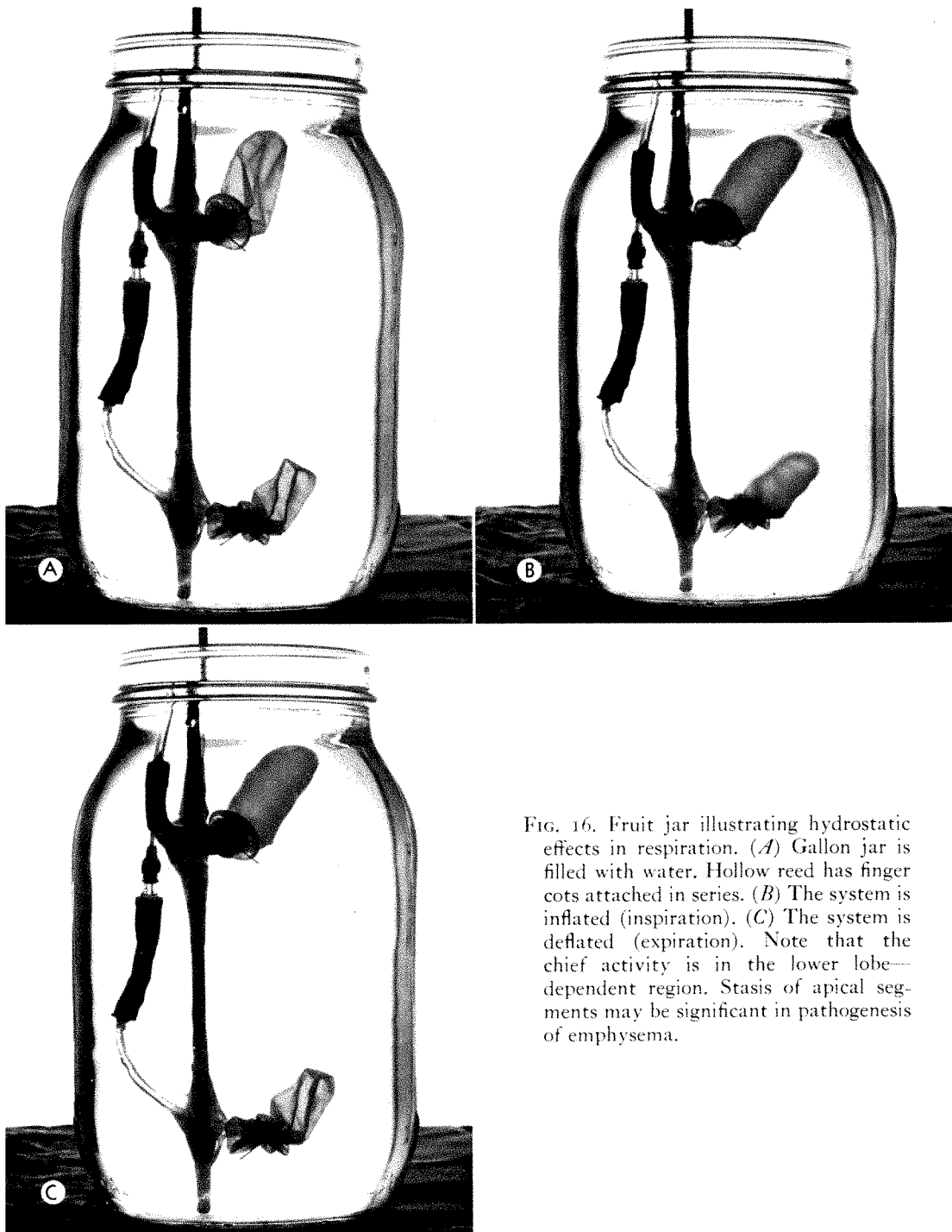


FIG. 16. Fruit jar illustrating hydrostatic effects in respiration. (A) Gallon jar is filled with water. Hollow reed has finger cots attached in series. (B) The system is inflated (inspiration). (C) The system is deflated (expiration). Note that the chief activity is in the lower lobe—dependent region. Stasis of apical segments may be significant in pathogenesis of emphysema.

ogs by incomplete ligation of the pulmonary artery. Bronchial arteries did enlarge in these animals.

We found the bronchial arteries enlarged and tortuous in children with emphysema

and cystic fibrosis. We cannot attribute these changes entirely to emphysema, since severe inflammatory changes were also present.

Our studies on thoracic morphology are

not conclusive but lead us to suspect some limitation of athletic prowess in students with certain thoracic conformities.

A hydrostatic role in the localization of centrilobular, panacinar, and bullous emphysema may exist. Hydrostatics and surface tension phenomena may combine in the development of "congenital" emphysema. We have confirmed the existence of such a hydrostatic factor by roentgen methods.

CONCLUSION

1. Chronic obstructive respiratory disease or pulmonary emphysema is an important disease which is subject to clinical and experimental study by radiologists.

2. "Asthma" is an important factor in the development of emphysema.

3. Bronchial arteries are abnormal in adult emphysema and in emphysematous cystic fibrosis in children.

4. Intrathoracic hydrostatic factors contribute to the development of pulmonary emphysema.

5. Chronic obstructive respiratory disease is a long-standing process, subclinical during most of its course.

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PULMONARY ARTERIOVENOUS SHUNTS IN EMPHYSEMA DEMONSTRATED BY WEDGE ARTERIOGRAPHY*

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IN MANY patients with emphysema, the blood arterial oxygen saturation is decreased at rest and may be still further diminished with exercise. Motley,^{14,15,16} Harris and Heath⁴ and others have demonstrated that this results primarily from the presence of poorly ventilated alveoli and the perfusion of blood through nonventilated areas of the lung. In most cases of severe emphysema, arterial blood oxygen saturation at rest may be improved by the intermittent positive pressure breathing of compressed air, which provides more uniform ventilation of alveoli, compared to that present during the breathing of ordinary room air. If many of the alveoli are destroyed or completely blocked, as for example by fibrosis, edema, mucus or any other factor, then intermittent positive pressure breathing may result in little or no increase in blood oxygen saturation. Under these circumstances, the breathing of a high oxygen mixture, which increases the partial pressure of the inspired oxygen sufficiently to overcome any significant alveolar-capillary membrane block, may not correct the blood oxygen desaturation. This failure to restore the arterial oxygen saturation to normal levels is indicative of perfusion of blood through nonventilated areas of lung which physiologically is equivalent to a right to left shunt. In severe emphysema this may become of considerable magnitude.⁴

Histologically, the most prominent vascular lesion in emphysema is the diminution

of the capillary bed, particularly about the respiratory bronchioles. Many capillaries are dilated, while others are obliterated.^{4,20} Intimal proliferation occurs in the thin walled arteries related to the terminal and respiratory bronchioles. Often these become thrombosed, following which they may be recanalized by capillaries from bronchial vessels. Notably, however, the changes in the muscular pulmonary arteries associated with high levels of pulmonary hypertension in mitral and congenital heart disease are rarely encountered in emphysema.

Normally, the pulmonary arteries, which are end vessels, communicate with the bronchial arteries only by means of the capillary bed in the respiratory bronchioles. In certain diseases, particularly bronchiectasis, the bronchial arteries become markedly enlarged and extensive anastomoses develop between the bronchial and pulmonary artery systems.^{5,8} In emphysema, this arterial collateral circulation is insignificant except when fibrosis or bronchiectasis is superimposed.¹¹ The venous collateral circulation, on the other hand, may be greatly expanded with the development of numerous anastomoses between pulmonary and bronchial veins. With right heart failure and elevation of pressure in the azygos system, Liebow *et al.*^{9,10,11} further state that there is the possibility of shunting of blood from the systemic to the pulmonary veins, *i.e.*, a right to left shunt. However, Heppleston and Leopold⁵ point

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out that, "As yet there is no certain means of judging whether the available channels were used during life and, if so, in which direction the blood flowed."

Numerous attempts have been made using histologic, injection and corrosion techniques to demonstrate direct pulmonary arteriovenous communications in both the normal lung and in various disease states, but there has been no definite agreement as to whether they actually exist. Injecting glass beads of known diameter, Prinzmetal, Ornitz, Simkin and Bergman¹⁹ concluded that there were arteriovenous anastomoses measuring from 100 to 390 micra in diameter in the normal lung. Similarly, Tobin and Zariquiey²³ perfused normal human lungs, with glass spheres up to 500 micra in diameter, and recovered them from the pulmonary veins. By latex injection studies they showed that these shunts were located at the apex of and within the lobular subdivisions of the lungs. Niden and Aviado,¹⁷ also using glass beads, showed arteriovenous communications of at least 420 micra in diameter in anesthetized dogs. Rahn, Stroud and Tobin²¹ injected thorotrast through a No. 11 catheter wedged in the pulmonary artery of normal dogs. They stated that arteriovenous shunts were visualized in 3 of 4 dogs but did not describe these shunts in any detail. On the other hand, Parker, Andersen and Smith¹⁸ could recover beads only up to 80 micra in diameter. They suggested that the recovery of larger spheres by other investigators may have been due to the use of excessive pressure of injection. James, Owen and Thomas⁷ could find no evidence of shunts over 30 micra in size in the absence of bronchiectasis and Gordon, Flasher and Drury³ could demonstrate none larger than 20 micra in rabbits. Liebow *et al.*⁸ have rather emphatically denied the existence of precapillary connections between pulmonary arteries and veins except in congenital hemangiomas.

However, more recently two excellent pathologic studies strongly suggest that pulmonary arteriovenous shunts do occur

in emphysema. Reid and Heard²⁰ injected the capillary network of normal and emphysematous human lungs with india ink and concluded that "in advanced centrilobular emphysema the side branches of the arteries or arterioles accompanying the affected proximal respiratory bronchioles are obliterated but the large vessels survive. These course through the area as isolated strands stripped of side branches but still patent and supplying the peripheral surviving networks of the lobule. When the latter capillaries are destroyed, one might suspect that surviving arterioles could carry arterial blood straight into venules and veins without communicating with alveolar or bronchiolar capillaries. Further work is needed to be sure that such communications do exist in emphysema and to discover their size." Describing the destruction of the capillary bed in centrilobular emphysema, Wyatt, Fischer and Sweet²⁴ found that "remnants of the pre-arteriolar bed had a mural course in the connective tissue canopies of bullae. Although rare, pathological shunting across these bullous spaces has been demonstrated, judged by genuine admixture of colored latex introduced from the main arterial and venous channels." Further, they found that in panlobular emphysema there was "extensive erasure of the capillary bed. With distention and disruption a widely spaced linear bed was formed. In the late stages, only a few large channels passed from the lobular arteriole to the paralobular veins."

The purpose of this paper is to report the visualization by wedge arteriography of pulmonary arteriovenous shunts in 3 patients with advanced pulmonary emphysema.

TECHNIQUE OF WEDGE ARTERIOGRAPHY

The technique of examination has been modified from that previously described⁶ only to the extent that in addition to the single-film arteriogram a second injection is now made for a cine-arteriogram. After the cardiac catheter has been wedged into a peripheral pulmonary artery, 2 cc. of 65 per

cent hypaque* is injected. The method of injection is the same whether the examination is to be recorded by a single roentgenogram or cineradiography.

Unless the catheter is properly wedged in the peripheral pulmonary artery, the arteriograms are usually of little value since very few of the smaller vessels will be visualized and the contrast medium may reflux into adjacent large vessels. The pressure monitor should be checked carefully to be sure that a true wedge pressure is being recorded. As pointed out by Bell *et al.*² in 1959, the catheter may lodge at the bifurcation of a vessel or impinge on a vessel wall and the resultant damped tracing may mimic a wedge tracing very closely. The position of the catheter should be verified by a slow hard injection of approximately 0.5 cc. of contrast medium.

Usually, it will be found that the catheter passes most easily into the right pulmonary artery and then most often into the right lower lobe. As a rule, this does not present a problem since the vascular changes in the lower lobes in most diseases can be expected to be as advanced as in any other portion of the lung. However, there are occasions, particularly in emphysema, where the pathologic changes are not evenly distributed and it may be desired to examine other regions of the lung. Unfortunately, it has been found that the catheter tends to pass repeatedly into the same peripheral vessel even when an effort is made to catheterize another area. To date, attempts to guide the tip of the catheter by means of an obturator have not been very successful.

Injection of Contrast Medium. Because of the rapidity with which the contrast material passes through the peripheral vascular bed, mechanical injection and automatic exposure are essential for standardization of the procedure. Injection may be made by hand but the results are inconsistent. The best arteriograms, both in single-film and cine-arteriography, are obtained when the 2 cc. of contrast material

are injected in 0.40 to 0.50 seconds. The applied pressure necessary to accomplish this will vary with the viscosity of the contrast medium, internal diameter of the catheter, the material of which the catheter is made, dimensions of the syringe, etc.* To eliminate the dead space, just before the actual injection is made, the catheter is filled by hand with contrast material under fluoroscopic control. The capacity of a No. 7 catheter is about 1.5 cc. After each injection, the catheter should be flushed immediately with saline.

Radiographic Technique. Non-screen film is used for single-film arteriography. A 10×12 inch film, either in a paper wrapper or cardboard holder, is laid directly on the patient's chest and the exposure made with the under-table tube automatically at the end of injection. It has been found that this is much simpler than attempting to place the film under the patient. It eliminates the use of an overhead tube, is more rapid, and permits more accurate centering and closer coning. The tube-film distance will vary from 30 to 40 inches, depending on the type of table and the thickness of the patient. No attempt is made to have the patient hold his breath during the procedure because many are heavily sedated, under anesthesia, or otherwise find it difficult to cooperate. The following exposure factors are used: Not more than 1/30 second to eliminate blurring, 300 to 400 ma., and 90 to 120 kv.

The cine-arteriogram is recorded on a fine grain film such as Eastman Kodak Linograph Shellburst at 60 frames per second. The cine camera is started as soon as the catheter has been filled and care taken that the injection is not made until the camera has come up to full speed.

No significant complications have occurred with the above technique. Mild paroxysmal cough, especially after multiple injections, may occur in children and

* Sodium diatrizoate, manufactured by Winthrop Laboratories, New York, N. Y.

* Peak pressures of approximately 250 mm. Hg have been measured during injection within the tip of a Statham Physiological Pressure Transducer Catheter, Model SF I. The pressure generated beyond the tip of the catheter has not been accurately measured.

less frequently in adults. Local staining may occasionally be seen but with saline irrigation this usually disappears in a few minutes. More than 2 cc. of contrast material should not be used. Injection of larger amounts of contrast medium may be followed by severe cough or even infarction.¹

OBSERVATIONS

It is not intended to describe in this paper the entire spectrum of the vascular changes in emphysema which have been demonstrated by wedge arteriography, but only to show that direct pulmonary arteriovenous shunts occur in this disease and that they can be visualized *in vivo* by this technique. When a 2 mm. artery or primary branch of a larger vessel is injected, a sharply defined oval, leaf-like network of vessels is opacified, consisting usually of a single central tapering artery from which arise numerous lateral arborizing branches (Fig. 1, *A* and *B*). On the single-film arteriogram, vessels as small as 100 micra in diameter can be seen distinctly. Smaller vessels, including the capillary bed, are recognized

only as a background blush. These small branching vessels include both arterioles and venules which are indistinguishable one from the other. The latter drain into collecting veins which surround the opacified segment. These in turn unite medially and empty into the left atrium. This entire complex of vessels seems to form a distinct vascular lobule and would appear to correspond to the vessels of the secondary pulmonary lobule.^{13,24}

Though individual vessels cannot be examined in as great detail nor as readily measured as they can on the single-film arteriogram, these anatomic features are clearly depicted in the cine-arteriogram. In addition, however, cine wedge arteriography does afford a means of studying the dynamics of the flow of contrast material through the peripheral pulmonary vascular bed. Of particular interest has been the flow of contrast material into the collecting paralobular veins. In the normal lung contrast medium will appear in these collecting veins on an average between 0.13 and 0.17 seconds after the beginning of injection. This arteriovenous transit time of hypaque

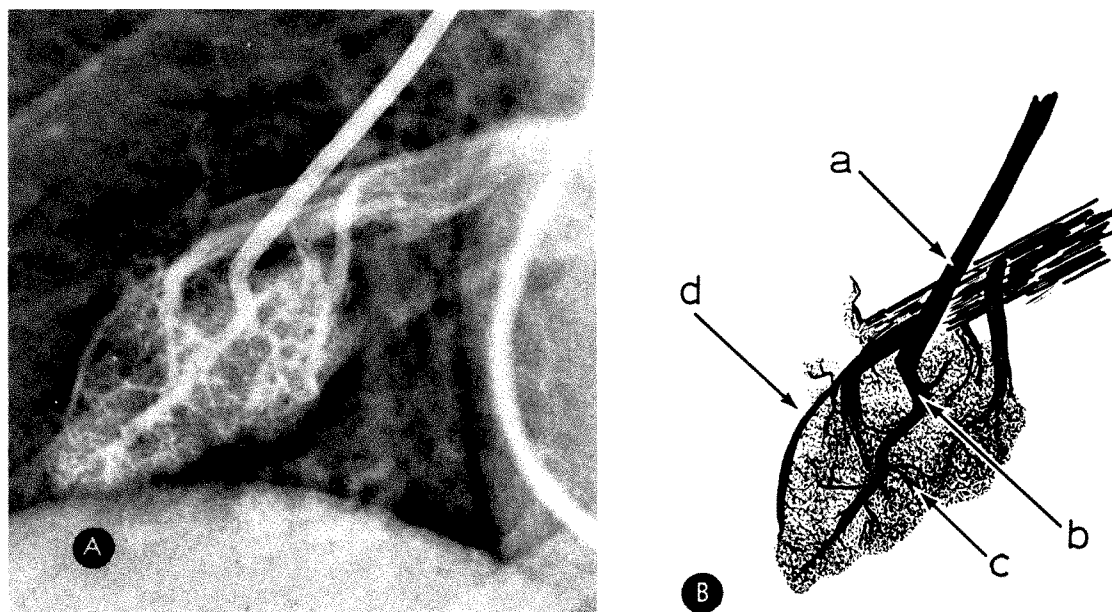


FIG. 1. (*A*) Normal wedge single-film arteriogram. (*B*) Diagrammatic sketch. (a) Wedged catheter. (b) Central artery of vascular lobule. (c) Arborizing branches and background (capillary) filling. (d) Paralobular draining veins.

is determined by counting the number of frames between the time the contrast material is first seen in the central artery to the time it can first be detected in a collecting vein, each frame being 0.0166 seconds in duration. It should not be assumed that the hypaque transit time and red blood cell transit time are necessarily the same.

In a number of wedge arteriograms obtained in patients with emphysema, the hypaque arteriovenous transit time was found to be more rapid than normal in spite of the fact that the arteriograms also showed a decrease in the number of small arborizing vessels and background filling. A careful study of the cine-arteriograms of several of these clearly showed this to be due to a flow of hypaque directly from the central artery or one of its branches into a parabolular vein without passage through an intervening capillary bed.

REPORT OF CASES

CASE I. G.G. (223-97-30), a 51 year old laborer, was first admitted to the Los Angeles County Hospital in September, 1962 because of acute respiratory infection. He gave a history of having had pneumonia 3 years previously and shortness of breath and cough for the past 2 years. Physical examination showed the chest to be increased in its anteroposterior diameter. The breath sounds were decreased and there

were rhonchi bilaterally. The electrocardiogram showed changes consistent with cor pulmonale and there was a partial right bundle branch block. The arterial carbon dioxide tension was 55 mm. Hg.

He was discharged after a short hospital stay and re-admitted in February, 1963 complaining of increasingly severe respiratory distress and dyspnea at rest. The blood pressure was 140/90 mm. Hg; hemoglobin 18.3 gm.; packed cell volume 56; white blood cell count 10,600.

The pulmonary function studies were indicative of marked obstructive airway disease (Table I). Arterial blood gas analysis (Table II) showed marked reduction in oxygen tension, increased carbon dioxide tension and respiratory acidosis. Breathing of 100 per cent oxygen caused the arterial oxygen tension to rise slightly. The calculated right to left shunt was 31 per cent. Cardiac catheterization showed moderate pulmonary hypertension (Table III). A No. 7 Cournand catheter was passed into the mid-portion of the right lung. The single-film arteriogram was entirely normal (Fig. 2, *A* and *B*). After flushing with saline, the catheter could not be replaced in the same vessel but passed into the base of the right lower lobe adjacent to the right atrium. The cine-arteriogram (Fig. 3, *A* and *B*) made in this region showed almost complete absence of arborizing branches and only a suggestion of a capillary bed. The hypaque flowed directly from the central artery into a parabolular vein from where it could be followed into the left atrium. The shunt at its

TABLE I
SELECTED DATA FROM PULMONARY FUNCTION STUDIES

Case No.	Vital Capacity		I Sec. Vital Capacity	Maximum Breathing Capacity	
	Observed (liters)	Per Cent Predicted	Per Cent N > 70	Observed (liters)	Per Cent Predicted
I. (G.G.)					
Room Air	1.94	42	29	30	22
After Isuprel	2.36	60	39	29	19
II. (J.C.)					
Room Air	3.41	93	38	54	47
After Isuprel	3.19	82	38	62	54
III. (S.F.)					
Room Air	2.36	63	51	38.8	39
After Isuprel	2.23	60	62	39.9	40

TABLE II
ARTERIAL BLOOD GAS STUDIES

Case No.	Oxygen Tension (mm. Hg)		Carbon Dioxide Tension (mm. Hg)		pH		Calculated Right to Left Shunt (% cardiac output) N = 2-4
	Room Air N > 100	100% Oxygen N > 550	Room Air N = 38-42	100% Oxygen N = 38-42	Room Air N = 7.38-7.42	100% Oxygen N = 7.38-7.42	
I. (G.G.)	45	132	72	67	7.353	7.33	31
II. (J.C.)	62	400	50	57	7.45	7.41	17
III. (S.F.)	—	—	48	—	—	—	—

TABLE III
SELECTED DATA FROM CARDIAC CATHETERIZATION STUDIES

Case No.	Mean Pulmonary Capillary Wedge Pressure (mm. Hg) N < 10	Pulmonary Artery Pressure (mm. Hg) N < 30/10	Oxygen Saturation (per cent)			
			Pulmonary Artery		Brachial Artery	
			Room Air N > 68	100% Oxygen for 3 min. N > 78	Room Air N > 96	100% Oxygen for 3 min. N = 100
I. (G.G.)	8	54/22	58	68	79	93
II. (J.G.)	8	40/25	64	70	90	100
III. (S.F.)	6	78/26	57	77	77	100

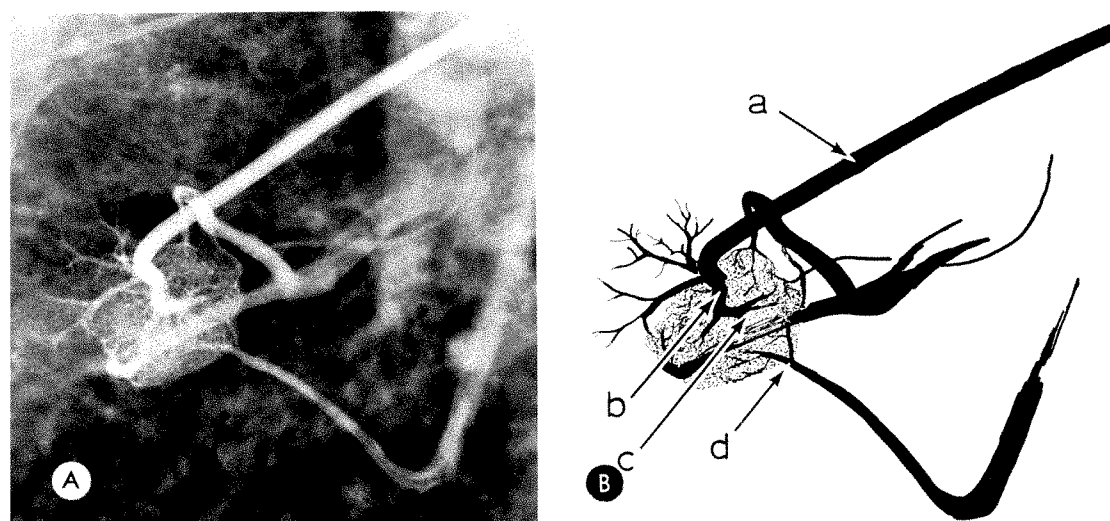


FIG. 2. Case 1. (A) Single-film wedge arteriogram made in the mid-portion of the right lung of a 51 year old male with severe emphysema. (B) Diagrammatic sketch. (a) Wedged catheter. (b) Central artery of vascular lobule. (c) Normal arborizing vessels and background (capillary) filling. (d) Paralobular draining veins.

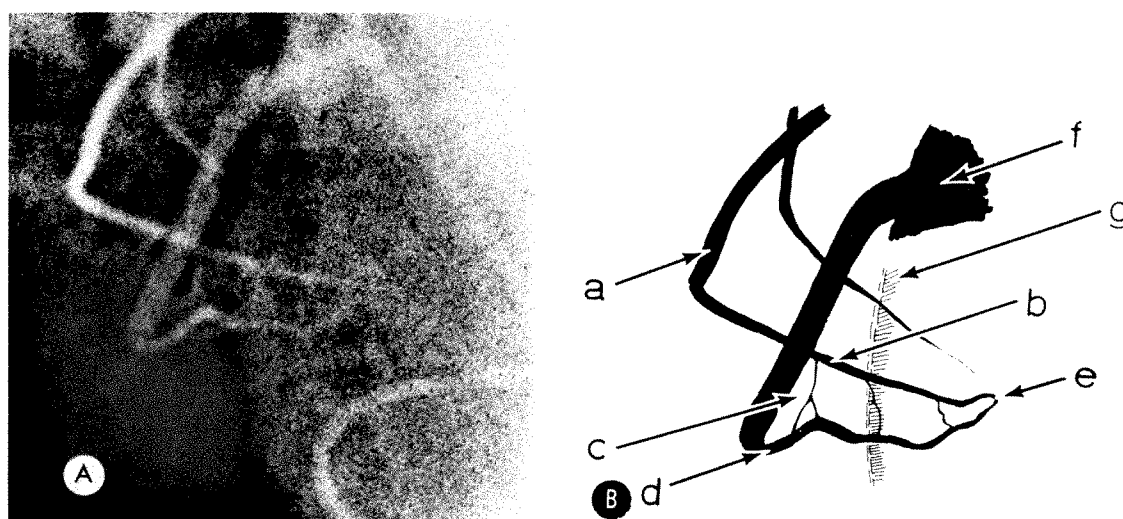


FIG. 3. Case I. (A) Frame of 16 mm. cine-wedge arteriogram made in right lower lobe. (B) Diagrammatic sketch. (a) Wedged catheter. (b) Central artery of vascular lobule. (c) Almost total absence of arborizing vessels and background filling. (d) The artery drains directly into a parabolular vein without passing through an intervening capillary bed. (e) The arteriovenous communication measures 570 micra at its narrowest point. (f) Draining vein emptying into the left atrium. (g) Right atrium.

narrowest point measured 570 micra in diameter (Table IV).

The patient was discharged after a short hospital stay. He was re-admitted for the last time in January, 1964. The arterial oxygen tension was 30 mm. Hg, carbon dioxide tension 52 mm. Hg and arterial pH 7.48. The arm to tongue circulation time was 30 seconds.

He died on January 15, 1964. Dr. Russell Sherwin of the Department of Pathology furnished the following description of the pertinent postmortem findings:

"Both lungs were moderately enlarged and hypercrepitant at the apices. There was moder-

ate bilateral subpleural bullous emphysema. An infarct was noted in the base of the right lower lobe in association with a fresh pulmonary artery thrombus. On cut section there was surprisingly little gross evidence of emphysema. Gough sections of the right lung showed irregularly distributed slight to moderate centrilobular and nonspecific emphysema, most marked in the apical one-half of the upper lobe. The distention primarily involved the respiratory bronchioles but areas intermediate between centrilobular and panlobular emphysema were common.

"The remaining autopsy findings were not re-

TABLE IV
WEDGE ARTERIOGRAPHY

Case No.	Hypaque Arteriovenous Transit Time (sec.) N = .13-.17	Arborizing Vessels	Background (capillary) Filling	Diameter* Pulmonary Arteriovenous Communication (micra)
I. (G.G.)	0.083	Markedly Decreased	Absent	570
II. (J.C.)	0.216	Slightly Decreased	Moderately Decreased	460
III. (S.F.)	0.17	Normal	Normal	660

* Corrected for magnification.

lated except for a moderate degree of right ventricular hypertrophy of the heart.

"Microscopic examination of the lungs revealed numerous early and organizing small thrombi in vessels of all calibers. There was a large infarct in association with a large vessel thrombus. Serial giant sections of the presumed site of the arteriovenous fistula were made but no arteriovenous anastomoses could be demonstrated. However, a few unusually dilated venules were found. Except for slight arteriosclerosis, no other vessel abnormality was noted. The emphysematous change was most prominent in respect to first and second levels of the respiratory bronchioles, with relatively little involvement of alveoli and alveolar ducts."

CASE II. J.C. (132-07-71), a 54 year old male, was admitted to the Los Angeles County Hospital in February, 1963, complaining of severe bilateral chest pain and increasing dyspnea of 5 days' duration. He gave a history of long-standing pulmonary tuberculosis, for which he had been hospitalized on numerous occasions in other institutions. The blood pressure was 110/70 mm. Hg, pulse 104, respirations 24. The physical examination showed the chest to be hyper-resonant and the breath sounds were diminished over the left thorax. A chest roentgenogram showed a pneumothorax on the left with 80 per cent collapse of the lung. The hemoglobin was 13.3 gm. and the white blood cell count 5,400.

The pulmonary function studies (after complete lung expansion had occurred) showed evidence of obstructive pulmonary disease (Table I). The blood arterial oxygen tension (Table II) was reduced at rest; the carbon dioxide tension and blood pH were elevated. After breathing 100 per cent oxygen, the arterial oxygen tension rose moderately but not to a normal level. At cardiac catheterization (Table III) the pulmonary artery pressure was normal. A No. 7 catheter was passed into the right lower lobe. The single-film wedge arteriogram (Fig. 4, *A* and *B*) showed a slight diminution in the number of arborizing vessels and a moderate decrease in background filling. After flushing with saline, the catheter was replaced in the same vessel and cine-arteriography was performed. Direct flow of hypaque from a branch of the central artery into a paralobular vein could be clearly seen in the upper portion of the vascular lobule. There was also a suggestion of a shunt in the lower portion of the vascular lobules. On the single-film arteriogram, the shunt was readily identified, the vessel measuring 460 micra in diameter at its narrowest point (Table IV). In the lower portion of the lobule, the vessel in question was identified but it was not certain that the appearance of a shunt was not produced by overlapping vessels.

CASE III. S.F. (217-77-93), a 65 year old male, was well until January, 1962, when he was first seen at the Los Angeles County Hospital com-

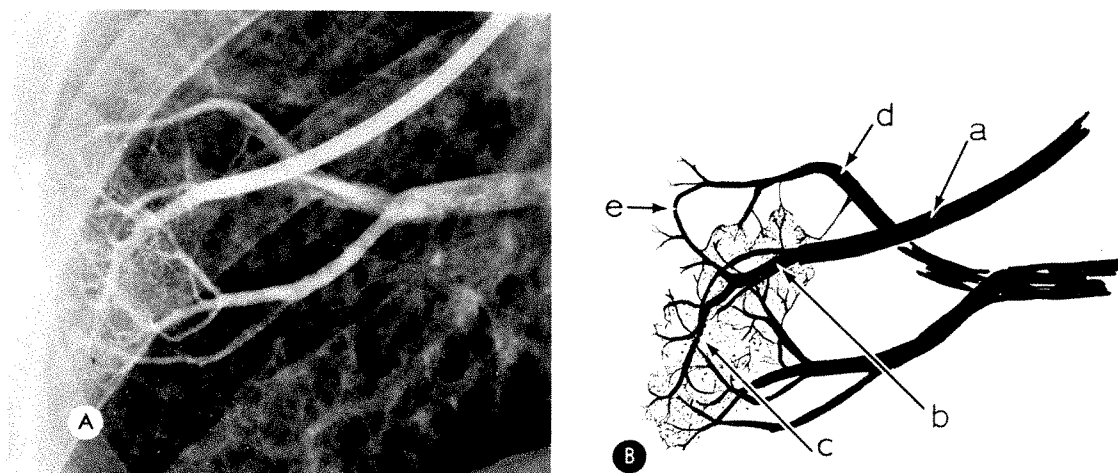


FIG. 4. Case II. (*A*) Single-film wedge arteriogram made in mid-portion of right lung of 54 year old male with advanced emphysema. Several vascular lobules are opacified. (*B*) Diagrammatic sketch. (a) Wedged catheter. (b) Central artery of vascular lobule. (c) Arborizing vessels are slightly decreased in number and there is moderate decrease in background filling. (d) The central artery drains directly into a paralobular vein. (e) At its narrowest point the arteriovenous communication measures 460 micra.

plaining of chest pain and ankle edema. The chest roentgenogram showed a slightly elevated left diaphragm; the lungs were clear and the heart was normal. The electrocardiogram was suggestive of chronic lung disease. He was treated for congestive heart failure and discharged. In July, 1963 he was re-admitted to the hospital because of chest pain, cough, increasing shortness of breath and orthopnea, and minimal ankle edema. The electrocardiogram showed extremely low voltage, peaked P waves and other changes suggesting diffuse pulmonary disease and cor pulmonale. A chest roentgenogram in August, 1963 showed widening of the superior mediastinum and infiltration in the right upper lobe. He did not return to clinic until January, 1964 at which time he complained of increasing shortness of breath and chest pain. Marked clubbing of the fingers had developed. He had moderate pitting edema of the ankles. The arm to tongue circulation time was 18 seconds. No tumor was seen on bronchoscopic examination; however, the sputum was positive for malignant cells.

Pulmonary function studies (Table I) were indicative of marked obstructive airway disease. His blood carbon dioxide tension was slightly elevated (Table II). At cardiac catheterization (Table III) he was found to have severe pulmonary hypertension and marked arterial oxygen desaturation at rest. A No. 7 Cournand catheter was passed into the right mid-lung but could not be properly wedged. The single-film

arteriogram showed filling of the central arteries of several lobules. The number of arborizing branches and the background filling were both moderately diminished. Cine-wedge arteriography (Fig. 5, *A* and *B*) was performed after the catheter was withdrawn and replaced in the right lower lobe. In this region the arborizing vessels were somewhat more numerous and the background filling fairly normal. Hypaque could be seen to flow directly from a branch of the central artery into a paralobular vein and thence into the left atrium. The smallest diameter of the shunt measured 660 micra (Table IV).

An exploratory thoracotomy was performed on March 9, 1964 and the patient was found to have an inoperable carcinoma of the left upper lobe. He died April 2, 1964. Postmortem examination was refused.

DISCUSSION

It is now generally held that pulmonary arteriovenous fistulae probably do not occur in the normal human lung. However, in the emphysematous lung, where pulmonary function studies and blood gas analyses may indicate the perfusion of nonventilated lung which is functionally equivalent to a right to left shunt, theoretically it would appear more likely that direct pulmonary arteriovenous communications should be present. The recent work of Reid and Heard²⁰ and Wyatt *et al.*²¹ lends strong sup-

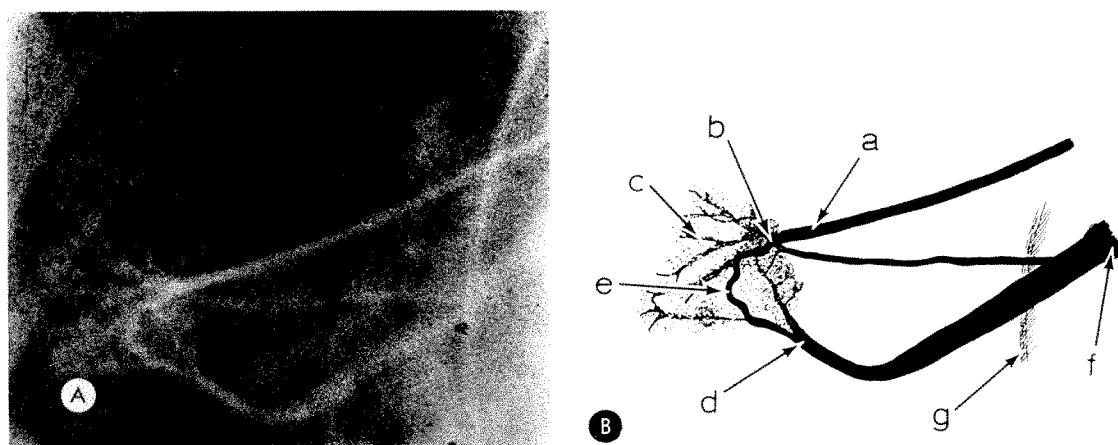


FIG. 5. Case III. (*A*) Frame of 16 mm. cine-wedge arteriogram made in the right lower lobe of 65 year old male with severe emphysema. (*B*) Diagrammatic sketch. (a) Wedged catheter. (b) Central artery of vascular lobule. (c) Normal arborizing vessels and background filling. (d) The central artery drains directly into a paralobular vein. (e) At its narrowest point this arteriovenous communication measures 660 micra. (f) Draining vein emptying into left atrium. (g) Right atrium.

port for their presence in emphysema, although up to the present time unequivocal proof for their existence is still lacking.

In the 3 patients with severe obstructive airway disease or emphysema included in this report during pulmonary wedge arteriography, hypaque was seen to flow from the peripheral pulmonary artery into which the catheter had been wedged directly into a pulmonary vein. These communications were clearly visible on the cine-arteriograms. In only 1 of the 3 cases were the single-film and cine-arteriograms made of identical sites and in this instance the same arteriovenous fistula was present. However, it was identified only in retrospect after first visualizing it on the cine-arteriogram. Both Reid and Heard and Wyatt have described relatively large vessels traversing emphysematous spaces which they believed were probably patent during life and constituted arteriovenous shunts. It is not unlikely that just such a vessel, almost completely devoid of all branches, was opacified in Case 1. In the other 2 cases, the direct arteriovenous communications were no less clearly present although the diminution of branching vessels and capillary bed was less marked, indicating the opacification of an area in which the vascular destruction was less severe. The question has been raised as to whether the anastomosis might be with bronchial rather than pulmonary veins. Fortunately, in both the first and third cases, the cine-arteriograms were made in areas sufficiently close to the heart so that the contrast medium could be seen to flow from the parabolular vein into the left atrium. There could be no doubt that the anastomosis was between pulmonary artery and pulmonary vein.

It is perplexing that these communications which are relatively easy to demonstrate by wedge arteriography should not be equally demonstrable by postmortem injection or corrosion techniques. Sherwin²² feels that it would have been impossible to adequately study the small arteries and arterioles in Case 1 by any of these methods because most of them were filled with

agonal thrombi. A tendency for these vessels to collapse after death and a further decrease in their size in fixed postmortem preparations may be additional factors preventing their demonstration.

In 2 of the 3 patients, sufficient data were available to calculate the proportion of pulmonary blood flow which was perfusing nonventilated lung. In 1 patient this right to left shunt was 31 per cent of the cardiac output and in the other, 17 per cent. Multiple arteriovenous fistulae, such as those which we have demonstrated, could be the means by which shunting of blood takes place in these patients with severe emphysema.

In spite of widespread capillary obliteration and consequent diminution of the total vascular bed, in severe emphysema marked pulmonary hypertension is unusual, though we believe that mild to moderate degrees of hypertension are more frequent than formerly suspected. It may be hypothesized that perhaps these shunts, offering little or even diminished resistance to blood flow, might serve as a protective mechanism, reducing the effect of the restricted vascular bed.

SUMMARY

1. The peripheral pulmonary vascular bed has been studied by wedge arteriography. The technique of single-film and cine-wedge arteriography is described. Vessels as small as 100 micra in diameter may be visualized and the flow through the peripheral vascular bed studied.

2. In patients with emphysema, there is often a reduction in background or capillary filling and a diminution in the number of small arborizing vessels.

3. Three patients with severe emphysema are reported in whom direct pulmonary arteriovenous communications have been demonstrated.

4. Pulmonary function studies and blood gas analyses indicate that hypoxia in pulmonary emphysema, at least in part, may be attributed to perfusion of blood through nonventilated areas of the lung. From these

studies, the existence of pulmonary arteriovenous shunts has been postulated but never before clearly identified *in vivo* or in pathologic specimens.

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ROENTGENOLOGIC PATTERNS IN LONG-STANDING BERYLLIUM DISEASE*

REPORT OF 8 CASES

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IN THIS article the development of unusual roentgenologic patterns seen in patients with long-standing beryllium disease is described. These patterns are illustrated by 8 case reports. Six were selected from 50 patients treated at the Massachusetts General Hospital. Two additional cases treated by colleagues elsewhere are also reported.

DIAGNOSIS

A major pathologic feature of chronic beryllium disease is a granulomatous interstitial inflammation of the lung, although other organs—kidney, liver, lymph nodes and skin—may also be involved with a similar pathologic process because of the widespread distribution of inhaled beryllium.^{6,9,11,20} In clinical descriptions the frequency of dyspnea, cough, and constitutional symptoms which have a variable and delayed onset from exposure to beryllium has been noted.^{5,13,14,15,19} Cyanosis, clubbing of the fingers and scattered inspiratory rales may be found in dyspneic patients. However, chest signs are often absent in spite of disability. Hyperglobulinemia, hypercalciuria, and hypercalcemia may occur as in patients with sarcoidosis. Respiratory function tests invariably show a “diffusion block” in disabled patients. These clinical features along with tissue assay or epidemiologic evidence of significant exposure to toxic beryllium compounds provide the basis for the etiologic diagnosis. The confirmatory diagnostic information may be obtained from a lung biopsy or an autopsy specimen. An interstitial granulomatous

pneumonitis, varying degrees of fibrosis, sometimes calcification of tissue, and distorted lung architecture may all be seen. Beryllium in the tissue specimen documents the clinical diagnosis; beryllium in the urine can only confirm an exposure to this element. The exposures of many patients seen at this hospital have been in the fluorescent lamp industry where beryllium fluorescent compounds were used from 1939 to 1949. Other cases have been reported from beryllium exposures in many other industries such as radio and x-ray tube manufacturing, ceramic laboratories, beryllium extraction plants, alloy manufacturing and the neon sign industry.

ROENTGENOLOGIC FINDINGS

Of special interest in this communication is the development of roentgenologic patterns in patients followed over many years. No attempt has been made to review the roentgenologic literature on this subject; however, in several articles the roentgenologic findings in acute and chronic beryllium disease are described.^{4,12,16,17,21}

The terms to be used in this description of the roentgenographic densities are granular, nodular, and linear. In earlier reports of roentgenographic abnormalities, these terms were often used to designate a stage in the duration or development of chronic beryllium disease. These terms have also been employed in other reports as if they represented qualitatively different pathologic changes, *e.g.*, a granuloma or an area of fibrosis. To make such specific inferences does not appear possible since no detailed

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correlative studies have been done. The densities reflect an interstitial inflammation of granulomatous character with or without varying degrees of fibrosis. This general statement can be made because there are adequate pathologic data at hand from biopsy and autopsy material.

ILLUSTRATIVE CASES

GRANULAR DENSITIES UNCHANGED (ROENTGENOLOGIC OBSERVATION FOR 15 YEARS)

CASE 1. L.F.K., a 24 year old man, was exposed to phosphors containing beryllium from March, 1941 to March, 1942. During the months following this exposure, he noted shortness of breath, cough, marked weight loss, and at times night sweats. Cervical lymph node biopsy showed only reticular hyperplasia. While his course initially appeared progressive, signs

and symptoms gradually subsided. In 1945 he passed a renal stone found to contain beryllium. Thereafter he passed a number of renal stones, 3 others of which contained beryllium. In 1955 hypertension and albuminuria were noted during a routine pre-employment examination. By 1959 he developed evidence of severe renal disease with uremia from which he died at the age of 43 in April, 1959. His long clinical remission from 1944 to 1959 and the unusual renal findings of an interstitial pyelonephritis have been previously reported.^{1,3}

Roentgenographic Description and Comments. Roentgenograms showed diffuse granular densities throughout. For the period of 15 years that he was observed, these granular densities remained sharply defined, about 0.25 to 0.5 mm. in diameter, and were evenly distributed (Fig. 1, A, B and C). The hilar shadows were prominent, indicative of enlarged lymph nodes. A

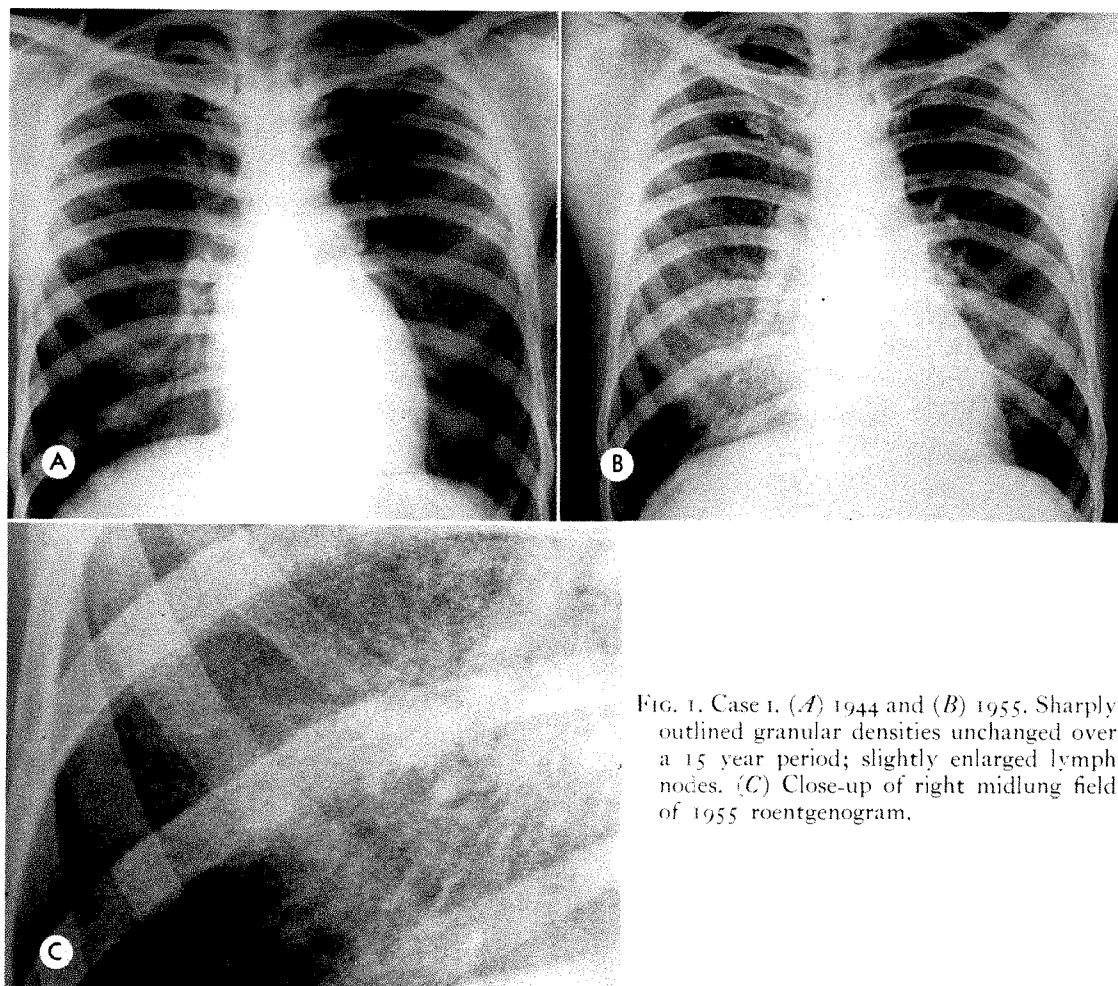


FIG. 1. Case 1. (A) 1944 and (B) 1955. Sharply outlined granular densities unchanged over a 15 year period; slightly enlarged lymph nodes. (C) Close-up of right midlung field of 1955 roentgenogram.

histologic examination was made of lung tissue obtained at autopsy. Granulomas scattered through normal intervening interstitial tissue were calcified.

The distinct outline of the small granular densities was attributed to calcification of the focal, well-circumscribed lung lesions. In a disease with a marked tendency to heal by replacement fibrosis, the persistence of these granular densities without visible change over 17 years is, in our experience, most unusual.

CONTRACTION OF UPPER LOBES (ROENTGENOLOGIC OBSERVATION FOR 17 YEARS)

CASE II. H.L., a 41 year old office worker, was first seen in 1947 because of cough and shortness of breath. Physical examination was initially normal. Tuberculin tests were negative. He had worked as a clerk at a fluorescent lamp manufacturing plant 4 years previously from 1940 to 1943. He was exposed to significant amounts of toxic beryllium compounds because of uncontrolled manufacturing operations in the adjacent work areas. His symptoms gradually increased. In 1949 persistent bilateral fine rales were noted. Respiratory function studies carried out at the Harvard School of Public Health and the University of Rochester showed a "diffusion block."^{2,7} In 1950 he received a course of ACTH with clinical improvement.⁸ He has since been treated with corticosteroids except for brief interruptions. He returned to work in 1953 when his dyspnea appeared controlled by therapy. Repeated measurement of respiratory function during the course of his illness has revealed persistence of his original "diffusion block" and later ventilatory impairment consistent with a clinical diagnosis of emphysema.

Roentgenographic Description and Comments. A roentgenogram of the chest in 1946 was negative (Fig. 2A). One year later there were early, but inconclusive, changes such as slight prominence of the bronchovascular markings and general haze in the lower lung fields. In 1948 and 1949 a definite diffuse nodular pattern, more prominent in the perihilar zones, was present (Fig. 2B). These nodules were ill-defined, measuring about 2 mm. in diameter. In the ensuing years there was a slight increase in the number and size of these nodular densities with a preponderance in the upper halves of both

lungs. There was a definite enlargement of the hilar lymph nodes.

From 1951 to 1963 contraction of the upper lobes took place with coalescence of nodules and their transformation into patchy densities, particularly on the left (Fig. 2, C and D). Streaky linear densities as well as emphysema with bullae formation accompanied this process. Both hilar areas became elevated and pleural thickening was seen. A few scattered nodules revealed incipient central calcification.

This case illustrates progressive pulmonary fibrosis with contraction of upper lobes accompanied by emphysema of lower lobes. This pattern, more often in a less advanced form, is seen in a number of cases of beryllium disease.

EMPHYSEMATOUS CYSTS OF UPPER LOBES (ROENTGENOLOGIC OBSERVATION FOR 14 YEARS)

CASE III. D.K., a 52 year old man, was working in a fluorescent lamp manufacturing plant and had been there since 1940. He first noted dyspnea and cough in 1952. A chest roentgenogram showed diffuse nodular infiltrates. He was placed on meticcorten with symptomatic improvement. Nine years later, in 1961, he had weight loss, fatigue, increase in dyspnea and repeated small hemoptyses. On two occasions he produced as much as 2 cups of blood. A second-strength PPD tuberculin test was positive, but numerous cultures and guinea-pig inoculations for *Mycobacterium tuberculosis* were negative. The Kveim test was negative. Bronchoscopy during an episode of hemoptysis showed blood coming from the left upper lobe. Lung function studies revealed a "diffusion block." The vital and total lung capacities were reduced to 53 per cent and 54 per cent of their predicted values while timed vital capacity was normal.

Roentgenographic Description and Comments. The first chest roentgenogram in 1949 was negative (Fig. 3A), but roentgenograms in 1951 and 1952 showed diffuse granular and nodular densities (Fig. 3B). A follow-up roentgenogram in 1957 demonstrated additional small linear densities as well as slight upper lobe contraction (Fig. 3C). At the time of the hemoptyses in 1961 and later (Fig. 3D), there was further contraction of the upper lobes. In addition, multiple bullae or cysts of varying size were interspersed throughout the upper lobes, more pronounced on the left. Some of them were actu-

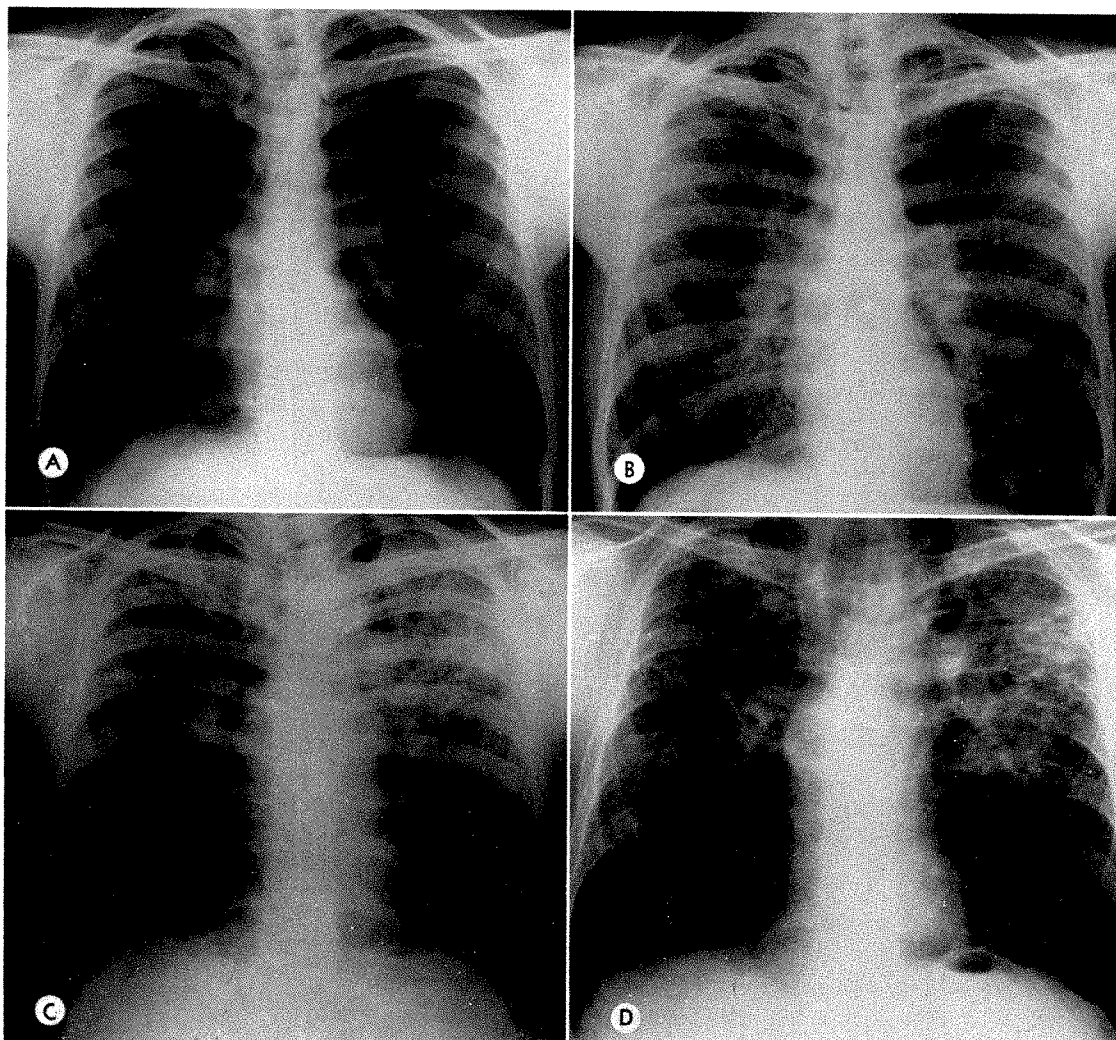


FIG. 2. Case II. (A) 1946. Negative. (B) 1948. Multiple nodular densities with slightly enlarged lymph nodes. (C) 1953 and (D) 1963. Conglomeration of nodular densities, contraction of upper lobes, pleural thickening, and basal emphysema.

ally bronchiectatic cavities. Both apices were encased in layers of thickened pleura, and there was deviation of the trachea to the right. The hilar shadows were distorted, slightly elevated and laterally displaced. Aside from the pattern of fibrotic and cystic changes, the original pattern of ill-defined granular, nodular, and reticular densities continued to persist, noticeably in the middle and lower lung fields.

CONTRACTION OF LOWER LOBES (ROENTGENOLOGIC
OBSERVATION FOR 15 YEARS)

CASE IV. S.M., a 42 year old woman, was exposed to beryllium compounds in a fluorescent

lamp manufacturing plant in 1942, first as a tube inspector and later as a laboratory technician analyzing beryllium-containing fluorescent powders. She remained in good health until 1953 when she developed fatigue, anorexia, and weight loss. At this time physical examination was unremarkable and tuberculin and Kveim tests were negative. Respiratory function studies in 1955 showed a "diffusion block" and a reduction in lung volumes. On meticorten she showed some improvement in respiratory function measurements. However, the improvement did not continue for studies in 1957 showed further diminution in lung volumes.

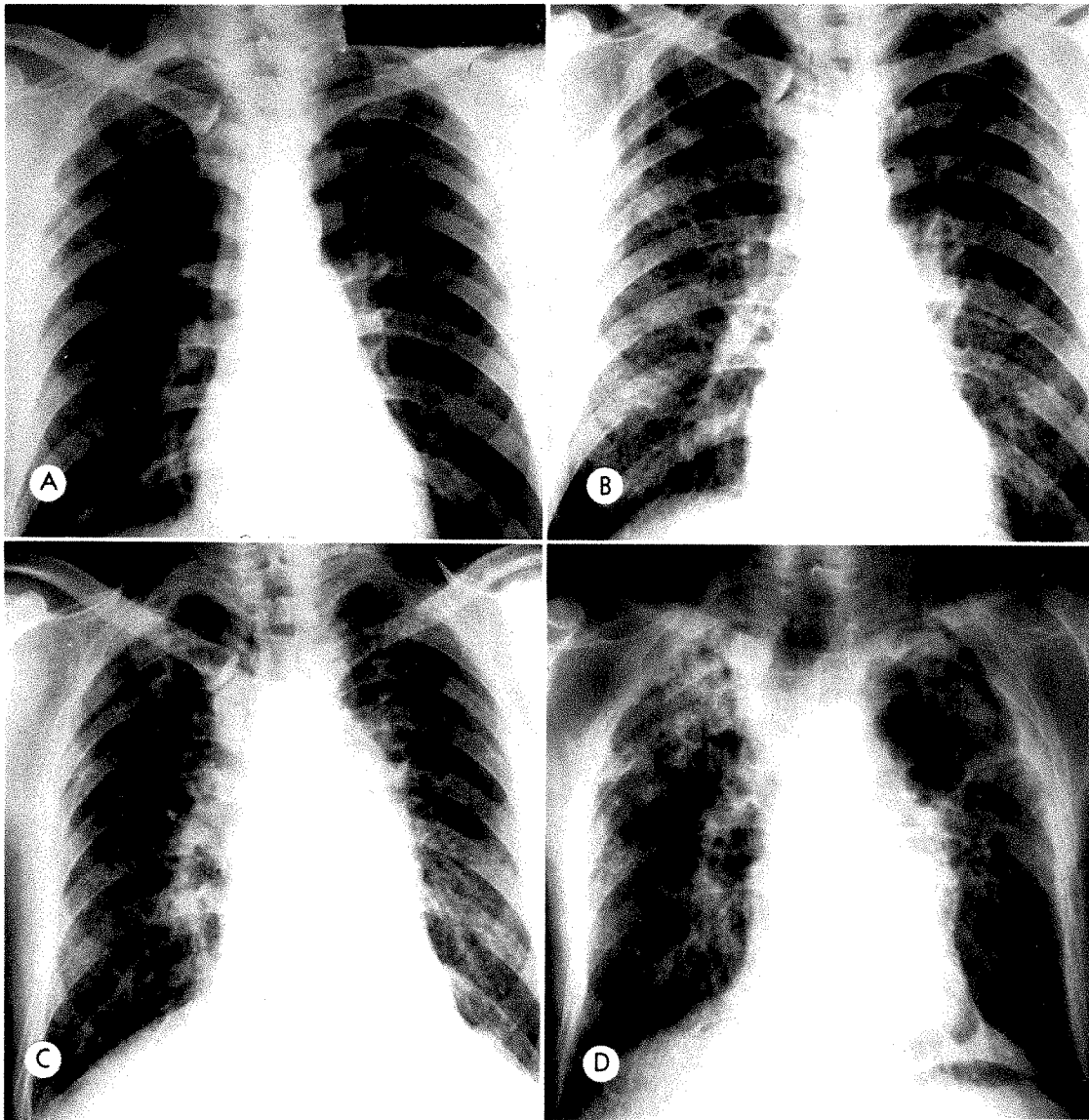


FIG. 3. Case III. (A) 1949. Negative. (B) 1951. Granular and ill-defined nodular densities in both lungs. (C) 1957. Early upper lobe contraction and scattered linear densities. (D) 1963. Marked upper lobe contraction, bullae, bronchiectatic cavities, and basal emphysema; pleural thickening with deviated trachea; persistence of nodular and granular densities.

Roentgenographic Description and Comments. The earliest roentgenograms, obtained in 1948 and 1953, were negative (Fig. 4A). In 1955 multiple granular and medium-sized nodular densities were seen in both lung fields except for the apices (Fig. 4B). Superimposed upon these nodules were a few linear densities in both lower lung fields. The minor fissure was displaced inferiorly due to a decrease in volume of the right middle and lower lobes.

Over a period of five years, there was a steady increase in the contraction of both lower lobes with a concomitant increase in the linear densities (Fig. 4, C and D). There was also a further descent of the minor fissure, corroborating the decrease in the volumes of the right middle and lower lobes. This was accompanied by compensatory upper lobe emphysema.

As in the previous case, these roentgenograms also illustrated progressive pulmonary fibrosis

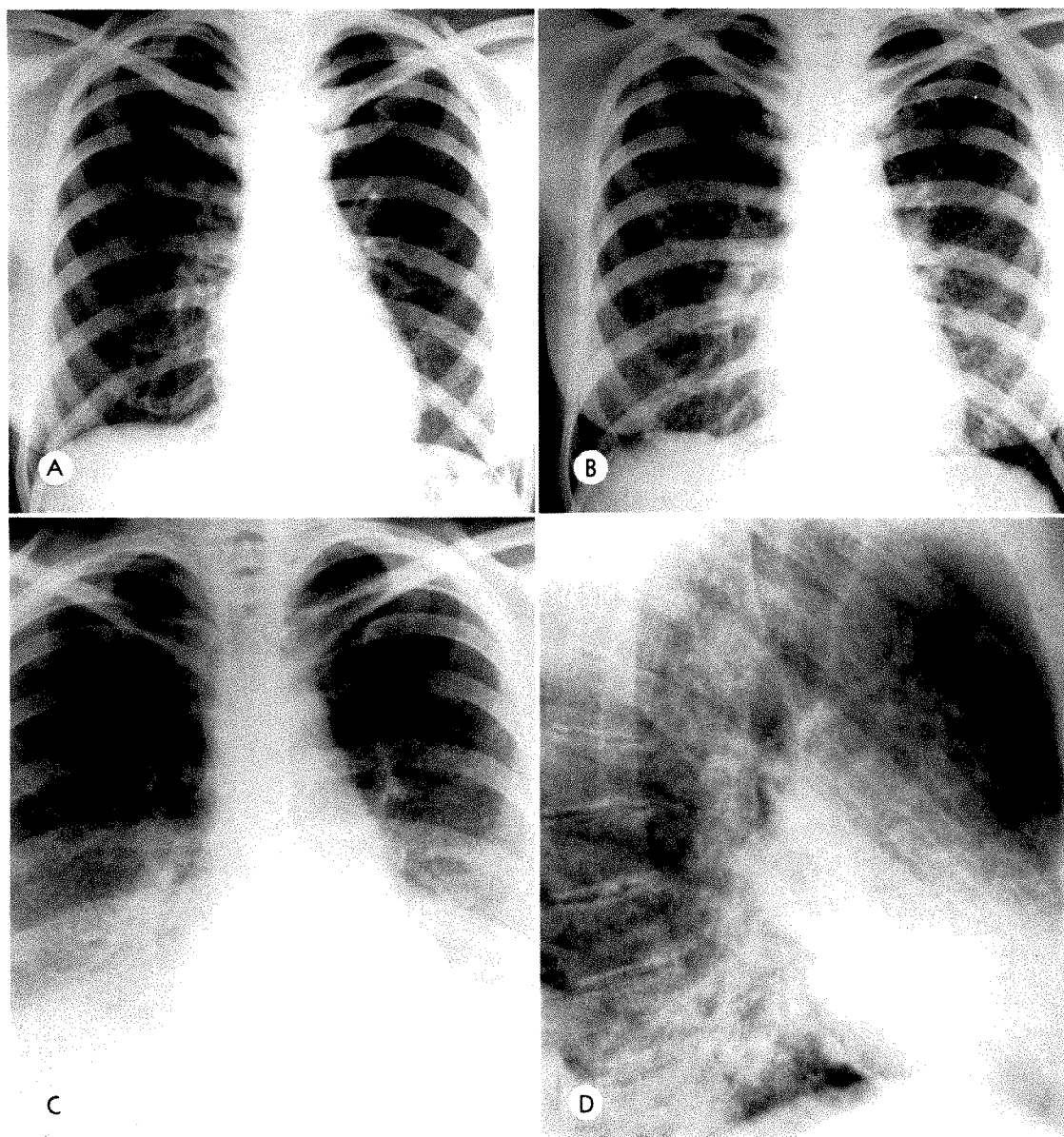


FIG. 4. Case IV. (A) 1953. Negative. (B) 1955. Granular and nodular densities in both lung fields. (C and D) 1963. Linear densities in both lower lobes with progressive lower lobe contraction.

but confined to the lower lobes. In our experience this pattern of contraction in the lower lung fields is rare.

EMPHYSEMATOUS CYSTS OF LOWER LOBES (ROENTGENOLOGIC OBSERVATION FOR 16 YEARS)

CASE V. N.I., a 41 year old patient, worked in a fluorescent lamp manufacturing plant from 1940 to 1945 where one of her jobs was breaking fluorescent tubes. She developed cough, dyspnea, and weight loss in 1943. Roentgenograms

showed diffuse nodular densities. By 1951 her symptoms had progressed so that she was placed on corticosteroids. By 1956 she had to give up her household duties. Her course was complicated by episodes of pleuritic chest pain, fever and increase in cough and sputa, as well as by repeated pneumothoraces. Hemoptysis was frequent and on one occasion a bronchoscopy revealed blood coming from the left upper lobe. Cor pulmonale developed and she died, after 17 years of illness, in March, 1960.

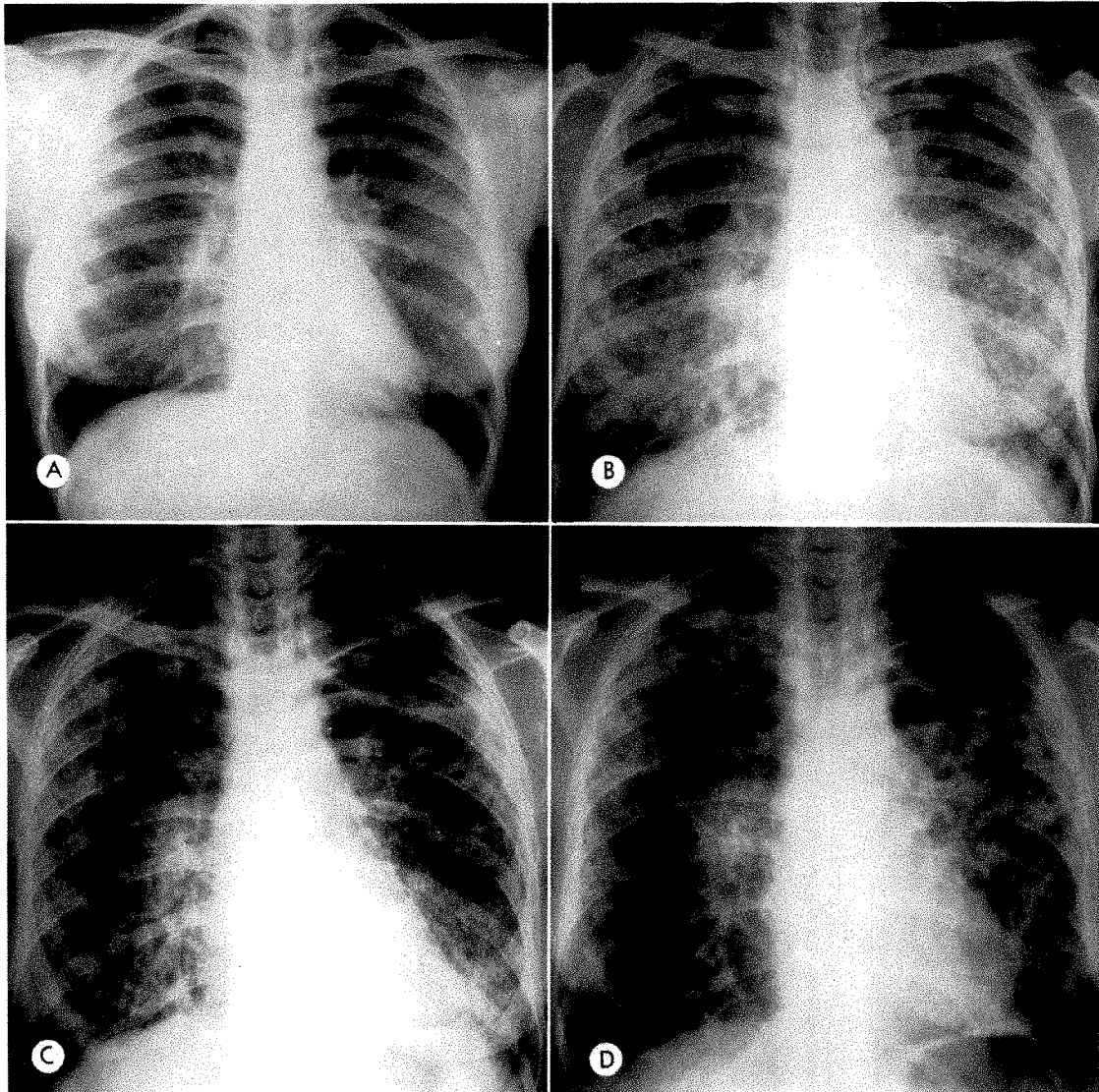


FIG. 5. Case v. (A) 1944. General haze of lung fields with early granular densities; slightly enlarged lymph nodes. (B) 1950. Mixed granular, nodular, and a few scattered patchy densities; small cysts in apices. (C) 1955. Increase in size of upper lobe cysts predominantly on left; linear densities are visible. (D) 1958.

Roentgenographic Description and Comments. The first chest roentgenogram in 1944 showed slight prominence of the hilar shadows, a general haze in the mid and lower lung fields and questionable early granular densities (Fig. 5A). In 1949 and 1950 multiple granular and poorly defined nodular densities were visible, accompanied by scattered small linear densities, small emphysematous cysts in both apices and slightly enlarged hilar lymph nodes (Fig. 5B). In 1955 there was a marked increase in size of the cysts or bullae in the left apex and to a lesser

degree in the right apex associated with generalized emphysema (Fig. 5C).

From 1955 to 1960 there was a marked increase in the number of cysts along with extension into the lower lobes (Fig. 5, D and E). With the emphysematous and bullous changes, conglomeration of the granular and nodular densities and increase in linear densities were present. A pneumothorax was noted in the 1960 roentgenogram.

Rupture of cysts was a frequent occurrence leading to pneumothoraces. This complication

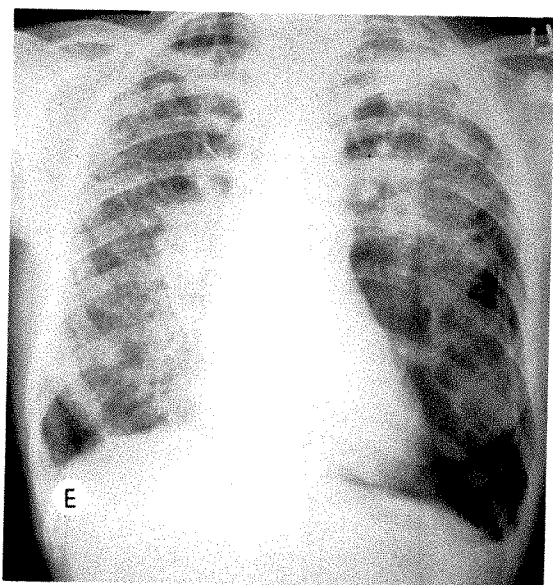


FIG. 5. Case v. (E) 1960. Extension of cysts into lower lobes with pneumothorax; linear opacities with distortion of hili.

is known to the Beryllium Registry in over 10 per cent of cases.¹⁹

Postmortem examination of the lungs revealed calcification within the nodular and granular densities. Extensive bullae formation with extension into the lower lobes was the predominant late change.

CALCIFICATION OF NODULAR DENSITIES (ROENTGENOLOGIC OBSERVATION FOR 9 YEARS)

CASE VI. C.M., a 38 year old housewife, worked at a fluorescent lamp manufacturing plant in the incandescent lamp division from

1943 to 1947. However, she had many contact with work areas involving the manufacture of beryllium-containing fluorescent lamps. She first noted dyspnea and cough in 1949. No clinical studies were done until 1954 when a chest roentgenogram was considered abnormal because of many fine nodular densities diffusely scattered throughout both lung fields. Respiratory function studies revealed a "diffusor block," reduction of her lung volumes, and slight impairment of timed vital capacity. Tuberculin and Kveim tests were negative.

In 1955 noncaseating granulomatous and interstitial pneumonitis consistent with beryllium disease was observed on lung biopsy specimens. Beryllium was present in the specimen. She was placed on meticorten with some improvement but has remained limited in her activities.

Roentgenographic Description and Comments.

A chest roentgenogram 7 years after exposure to beryllium showed diffuse ill-defined nodular and interlacing linear densities (Fig. 6A). The lymph nodes were slightly enlarged with scattered calcifications.

In the ensuing years, follow-up roentgenograms demonstrated small calcified foci within the central portion of the original parenchymal nodules. The calcification involved the core of the nodule, leaving a low-density halo and was most pronounced in the densities of the upper lung fields. It had developed gradually over many years, and was best seen on the latest examination in 1963 (Fig. 6B).

We have seen calcification in parenchymal nodules to even a greater degree in

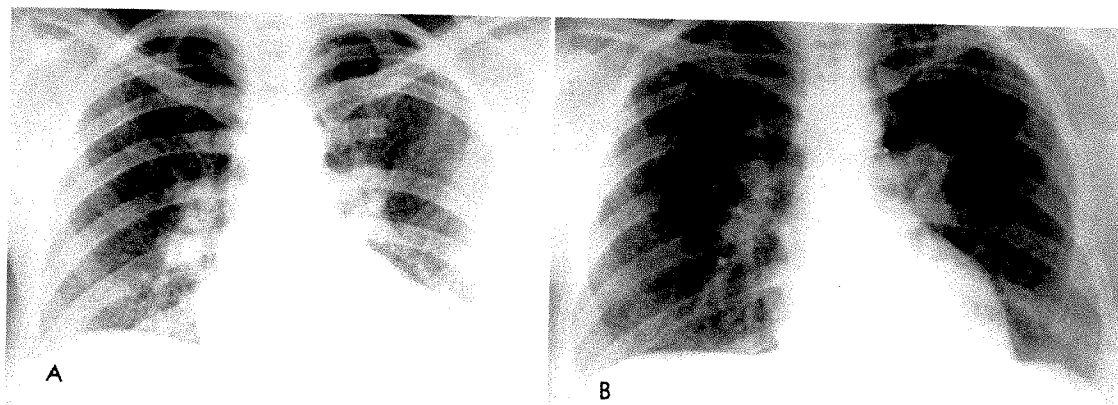


FIG. 6. Case VI. (A) 1955. Multiple nodular densities with slightly enlarged lymph nodes. (B) 1963. Slight degree of nodular calcification predominantly in upper lung fields.

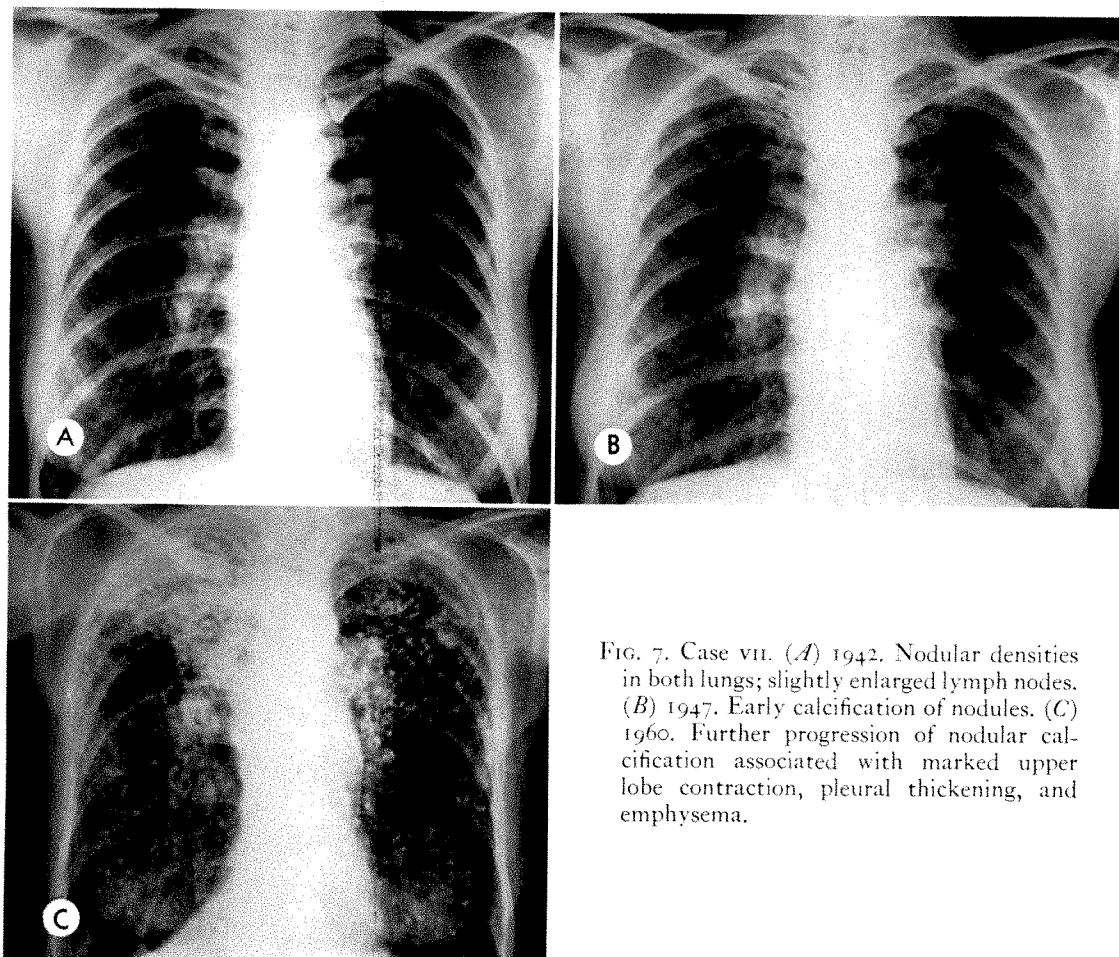


FIG. 7. Case VII. (A) 1942. Nodular densities in both lungs; slightly enlarged lymph nodes. (B) 1947. Early calcification of nodules. (C) 1960. Further progression of nodular calcification associated with marked upper lobe contraction, pleural thickening, and emphysema.

several cases of which the following is the most marked example.

CALCIFICATION OF PARENCHYMAL NODULES WITH
STONE FORMATION (ROENTGENOLOGIC OBSERVA-
TION FOR 18 YEARS)

CASE VII. K.S., a 52 year old woman, worked on radio tubes between the ages of 16 and 27. Work included wiring tubes, welding parts, and mounting grids coated with beryllium. At the age of 28, she noted shortness of breath, cough, and weight loss. Roentgenograms showed diffuse nodular densities. Histoplasmin and tuberculin skin tests were negative.¹⁸ Her condition gradually deteriorated, and eventually she was confined to a wheel chair. She coughed up small lung "stones" which were found, on spectrographic study, to contain beryllium. She died in respiratory failure in 1963.

Roentgenographic Description and Comments.

On the initial chest roentgenogram in 1942, obtained 12 years after the first exposure, there were diffuse small nodular densities in both lung fields along with slight enlargement of hilar lymph nodes (Fig. 7A). A few nodules contained central areas of calcification (Fig. 7B). The calcification of the nodules was progressive, and on the latest roentgenogram in 1960, most of the nodules were entirely replaced by calcium densities (Fig. 7C). Concomitant with this process of calcification were upper lobe contractions with elevation of both hili, apical pleural thickening, particularly on the right, and basal emphysema.

This case illustrates the extent to which the calcific process may progress, replacing the entire nodule, whereas in other cases, for example Case VI, the process was less extensive. In our experience calcification

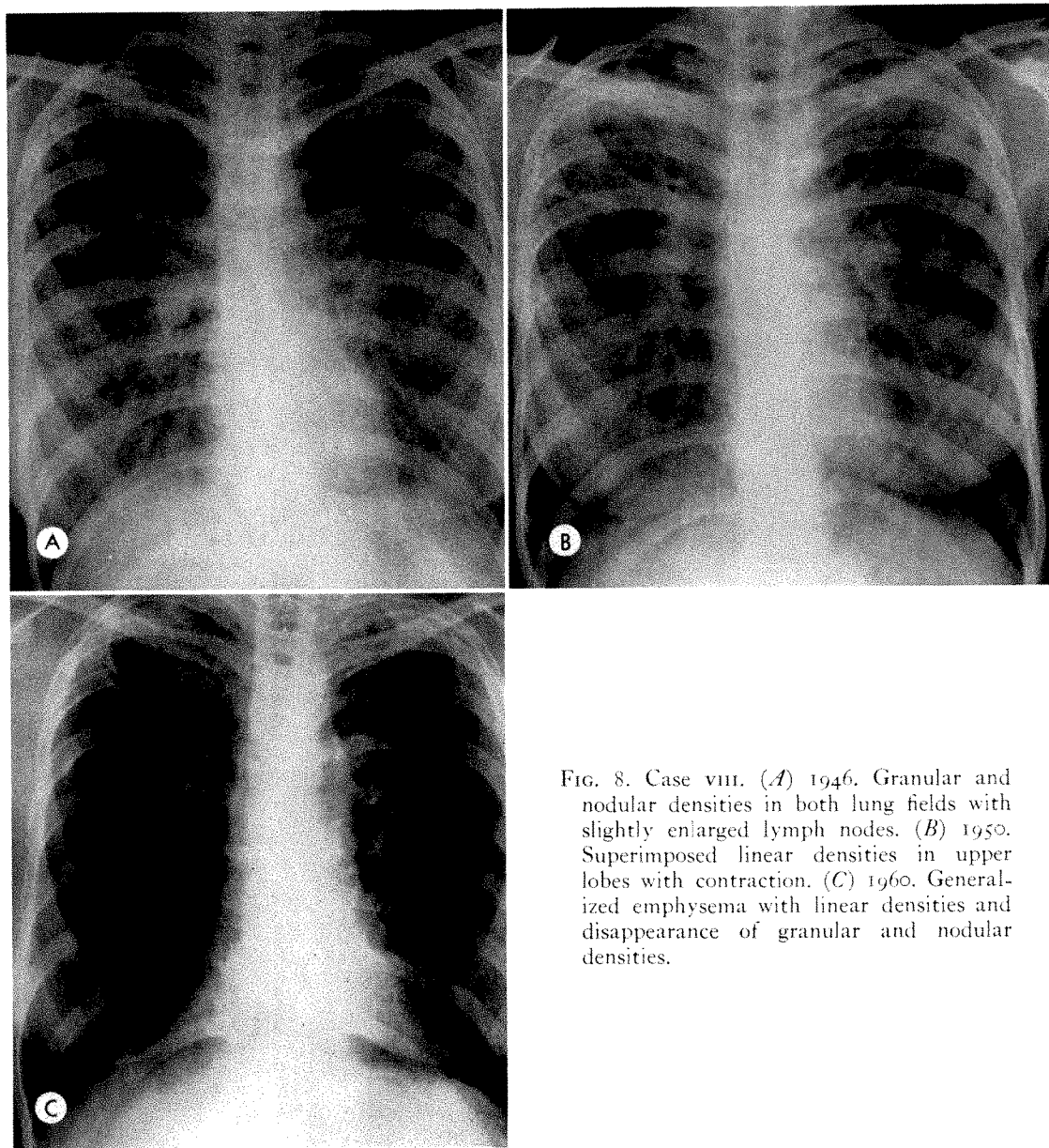


FIG. 8. Case VIII. (A) 1946. Granular and nodular densities in both lung fields with slightly enlarged lymph nodes. (B) 1950. Superimposed linear densities in upper lobes with contraction. (C) 1960. Generalized emphysema with linear densities and disappearance of granular and nodular densities.

has occurred more commonly in beryllium disease than in sarcoid.

DISAPPEARANCE OF NODULAR DENSITIES, DIFFUSE
EMPHYSEMA, AND UPPER LOBE CONTRACTION
(ROENTGENOLOGIC OBSERVATION
FOR 17 YEARS)

CASE VIII. F.A., a 42 year old female, worked in the fluorescent lamp industry from 1939 to 1943. In 1944 at the age of 22, she complained of cough, dyspnea, and weight loss. Symptoms rapidly progressed so that by 1946 she was a

bed and chair patient. A pneumothorax complicated her disease in 1947 and 1954. Cor pulmonale and congestive failure supervened in 1962. Since 1951 she has been treated with corticosteroids.

Roentgenographic Description and Comments. Roentgenograms made in 1945 and 1946 showed diffuse, evenly distributed nodular densities, interspersed with numerous granular densities (Fig. 8A). The lymph nodes were slightly enlarged.

In 1948 slight increase in size was noted in the

nodular densities in the upper lung fields. In 1950 there was slight conglomeration of the upper lobe shadows with a few superimposed linear densities (Fig. 8B). Both upper lobes were slightly contracted and both hili were elevated.

In 1960 the granular and nodular densities were not visible. There was diffuse emphysema with upper lobe contraction (Fig. 8C). Fine linear densities were scattered throughout the emphysematous lung fields.

This case demonstrates the disappearance of granular and nodular densities on the roentgenogram to a point where by roentgenologic means diagnosis is not readily possible.

DISCUSSION

The reported 8 cases, observed for up to 18 years, illustrate the development of unusual pulmonary patterns in long-standing beryllium disease.

The pulmonary changes consisted of granular, ill-defined nodular and linear densities occurring singly and in combined forms. Lymph node enlargement, slight to moderate in degree, accompanied these lung densities in 6 out of the 8 cases reported here. A mixed pattern of granular and nodular densities was most commonly seen. In Case I, the persistence of granular densities alone, unchanged over a period of 18 years, is a most unusual pattern and rarely observed. That calcification of different densities may take place in beryllium disease is not generally appreciated. This finding we have observed in several cases. The extent and degree of nodular calcification vary as illustrated by Cases VI and VII. Pathologic studies reveal that such calcification of nodules may be present (Cases I and V) although not seen on roentgenograms.¹⁰ Small and scattered linear densities often develop in the course of years. In advanced cases, linear densities may be very marked and associated with contraction of segments and lobes, conglomeration of nodular densities, and emphysema with bullae formation (Cases II to V).

Such roentgenologic changes most fre-

quently involve the upper lobes. In contrast, similar fibrotic changes confined to the lower lobes (Case III) are very rarely seen. The formation of large bullae in the lower lobes as in Case V is likewise very infrequent. When hemoptysis occurs, the question of whether such cysts are tuberculous cavities becomes a clinical issue. In 3 well-studied cases an acid-fast infection was ruled out completely.

Concomitant with the fibrotic and emphysematous lung changes, there may be a diminution in the number of granular and nodular densities to a point where a roentgenologic diagnosis of beryllium disease is not considered (Case VIII).

SUMMARY

A roentgenologic study of 8 cases of chronic pulmonary berylliosis is presented. A brief history of each case is outlined along with a discussion of the development of patterns of roentgenographic changes seen after many years of follow-up observation.

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EXPERIMENTAL KIDNEY LACERATION, RUPTURE, AND AMPUTATION*

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BLUNT or penetrating trauma to the abdomen or flank is a common occurrence.^{1,3,4,7,8,9,10,12,13,14,16} Vital bodily functions are often disturbed and organ systems may be temporarily or permanently damaged. An injury of the abdominal wall or flank may be accompanied by serious lesions of the viscera without any visible sign of injury to the abdominal wall. The solid viscera of the abdomen (liver, spleen, pancreas and kidneys) are particularly vulnerable to injury. Pathologic states such as tumor, hydronephrosis or over-distended bladder predispose these organs to traumatic injury.

In general, intravenous pyelography may demonstrate a deformed renal pelvis due to compression by intrarenal hematoma or compression of the kidney or pelvis by an extrarenal hematoma. Deformation may also be caused by a blood clot, or two or more of these factors in combination. The demonstration of extravasation of contrast medium from the renal pelvis into the parenchyma or outside the kidney provides a conclusive sign of rupture.¹¹

In recent years, angiography has been used to evaluate renal trauma.⁵ In 1963, Olsson and Lunderquist¹¹ performed renal angiography on 5 cases of acute renal trauma. In 1 patient no change was found on angiography. In 3 patients the kidney was displaced by perirenal hematoma but no evidence of true renal rupture could be demonstrated. In only 1 patient, the examination revealed the presence and extent of renal rupture.

In 1963 Čapek and Fojtík² reported 4 cases with angiographic documentation; in 1 case trauma to the lower pole of the kidney was defined by a hazy area of ischemia

involving the medulla and cortex. The arterial phase failed to reveal the problem. A second case, once again on nephrogram effect, showed a rather vague ischemic area defined against the surrounding well opacified parenchyma. A third case showed compression of the renal parenchyma with spreading of the renal artery branches and gross displacement laterally of the capsular artery, markedly distorted by the large intracapsular hematoma.

Hemley and Finby⁶ reported 2 patients with renal trauma and involvement of the main renal artery. In 1 patient, thrombosis of the renal artery resulted in almost complete occlusion. In the second patient, there was diminution of artery size and number of branches.

PROCEDURE

Our animals were prepared by using the Seldinger¹⁵ technique of retrograde femoral artery catheterization. The dogs were then laparotomized and prepared for kidney trauma in the dog laboratory, and were then transported to the radiologic special procedure room.

Trauma was inflicted by three methods. First, by crushing the kidney between two flat instruments until laceration occurred in the outer aspect of the kidney. The amount of resulting trauma ranged from minimal laceration in the capsule and parenchymal crush to extensive laceration of the capsule and crushing of the cortex and medulla. The second method employed was incision of the capsule and of the immediately underlying parenchyma, with subsequent deepening of this by using the handle of the scalpel (Case 1, Fig. 1 through 4). By this means, the depth and extent of

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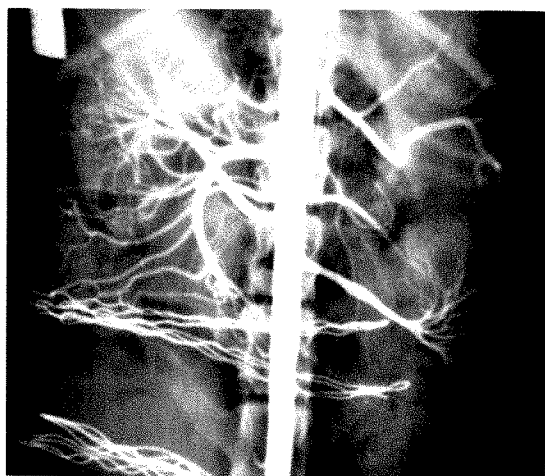


FIG. 1. Case 1. Early study in arterial phase. Immediately prior to study an incision was made through the capsule and peripheral cortex, then deeply extended by using the handle of a scalpel to the depth of three-quarter inch. The opened plane of the injury faced the roentgen-ray beam. Little disturbance in the arterial branches is seen.

injury was controlled. The third method was direct amputation of a segment of kidney.

Following trauma, retrograde aortic injections were performed to evaluate the main renal arteries, renal artery branches

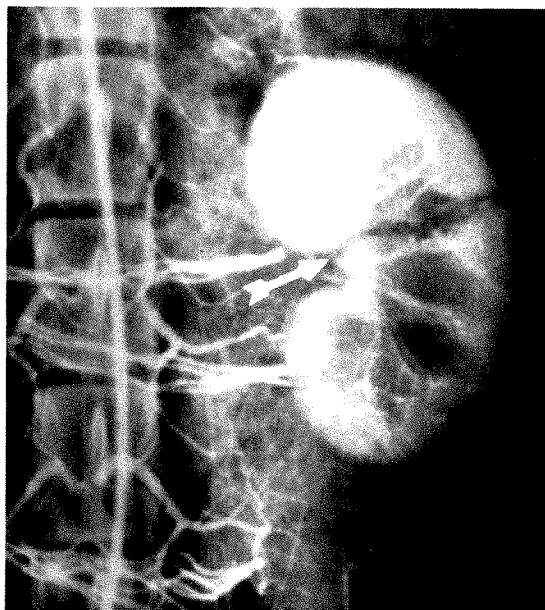


FIG. 2. Case 1. Nephrogram phase showing deep cleft in the kidney at site of capsule incision.

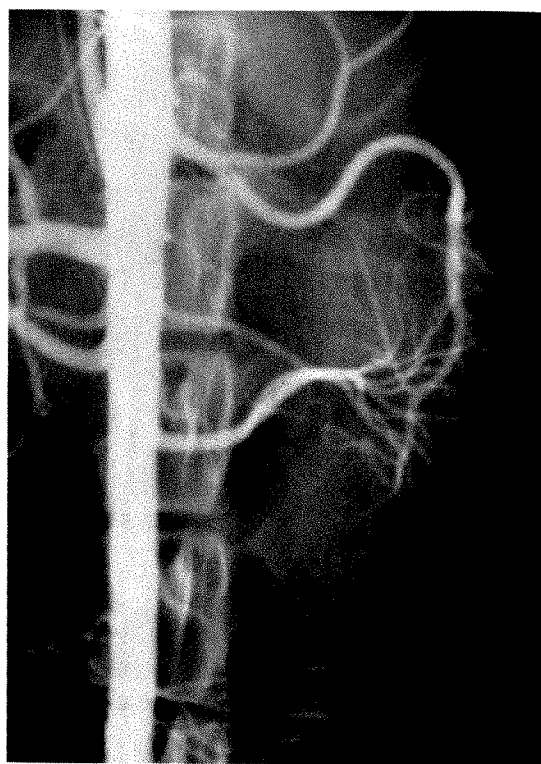


FIG. 3. Case 1. One week following trauma, arterial branching appears normal.

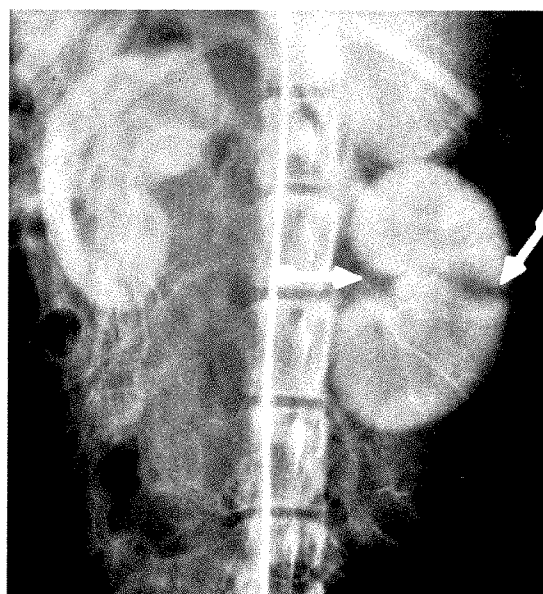


FIG. 4. Case 1. Nephrogram phase again demonstrates deep cleft in kidney parenchyma. The margins of the lesion are hazy indicating onset of healing.

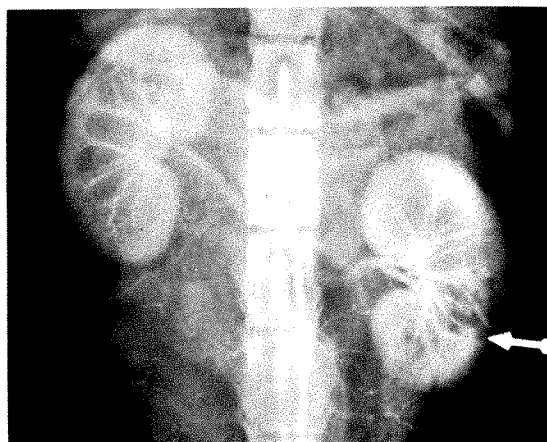


FIG. 5. Case II. Roentgenogram following extensive trauma across ventral surface of lower half of kidney. Small seriation is noted on nephrogram in lower pole. Overlying normal parenchyma obscures the lesion to great degree. Defects are best seen in cross section rather than *en face*.

and kidney parenchyma. Early in the film series, that is, in the first 2 seconds, the arteries and their branches are most clearly defined. As filming continues, the kidney parenchyma receives the main bolus of contrast material and the nephrogram effect becomes the most prominent. The most minimal changes are seen reliably only during the nephrogram phase (Case III, Fig. 6 through 10). The kidney parenchyma adjacent to the capsule involved by the lesion loses its sharp outline and the nephrogram effect tends to decrease. If the defect is broad and deep and facing the roentgen-ray tube in cross section, it will be seen. If the lesion is not seen in cross section, *i.e.*, if the roentgen-ray passes through considerable normal tissue dorsal and ventral to the plane of injury, the injury may not be visualized (Case II, Fig. 5). As the defect increases in size, the chances of demonstrating the lesion during the arterial phase increases. Displacement of the collecting system and capsular arteries will necessarily depend to a degree upon an intact capsule which will retain the parenchymal hemorrhage.

When a portion of the kidney is amputated, the arterial supply is abruptly interrupted; thus it is well shown during

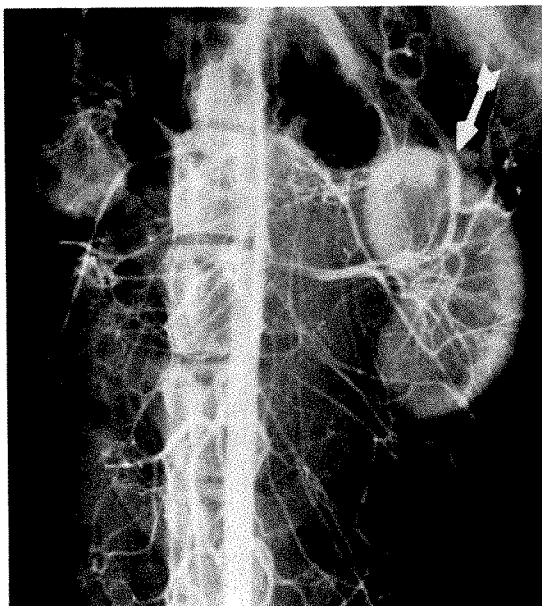


FIG. 6. Case III. Roentgenogram made immediately following laceration $1\frac{1}{2}$ inches long. Note defect in cortex in early nephrogram phase. Cleft partly covered by a filled vessel.

the arterial phase (Case IV, Fig. 11 and 12; Case V, Fig. 13 through 16). The remaining kidney is well outlined in the nephrogram phase. Extravasation of contrast material

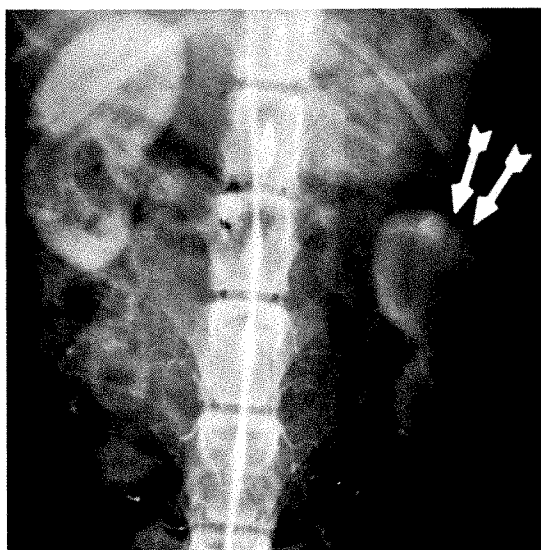


FIG. 7. Case III. Seven weeks post trauma, 2 lucent clefts are seen in the nephrogram phase. The margins of the defects are less sharp, demonstrating early healing.

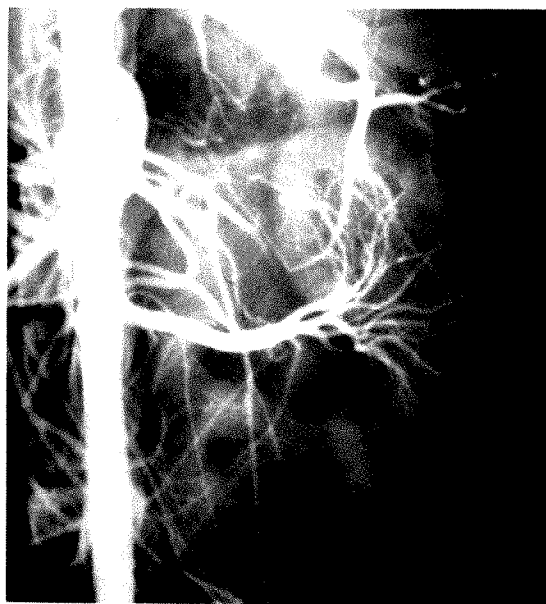


FIG. 8. Case III. Thirteen weeks post trauma; early arterial filling is demonstrated. Little clue to the trauma is seen. Main vessel branches are not disturbed.

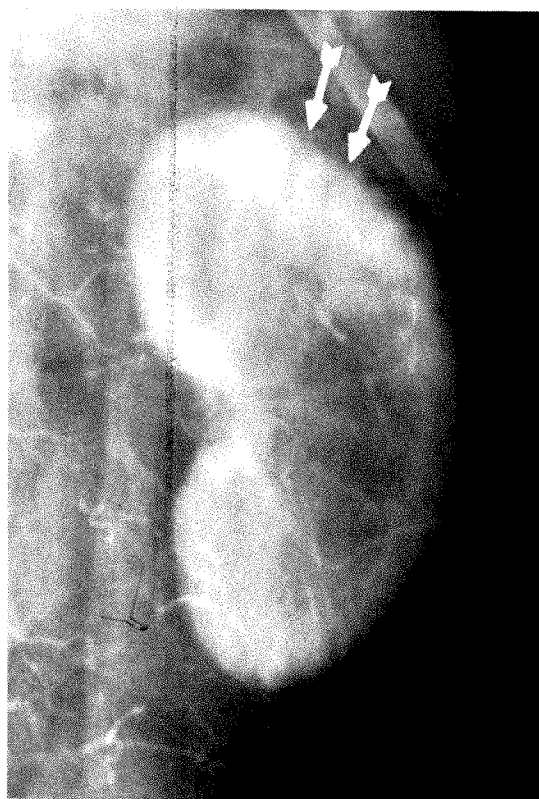


FIG. 10. Case III. Close-up view of injured cortex in late nephrogram phase. Irregularities extending into the cortex are demonstrated as well as a loss in smooth outer contour of cortex.

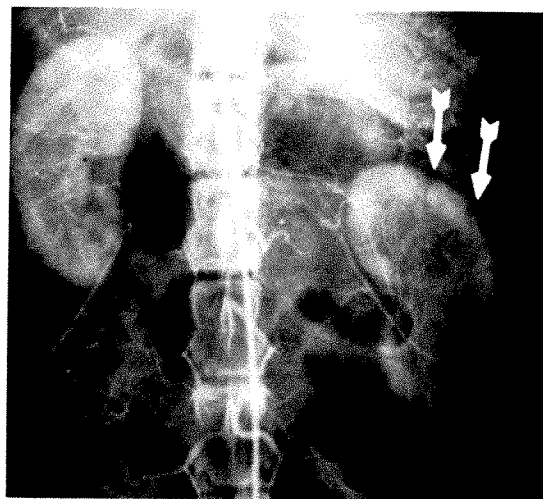
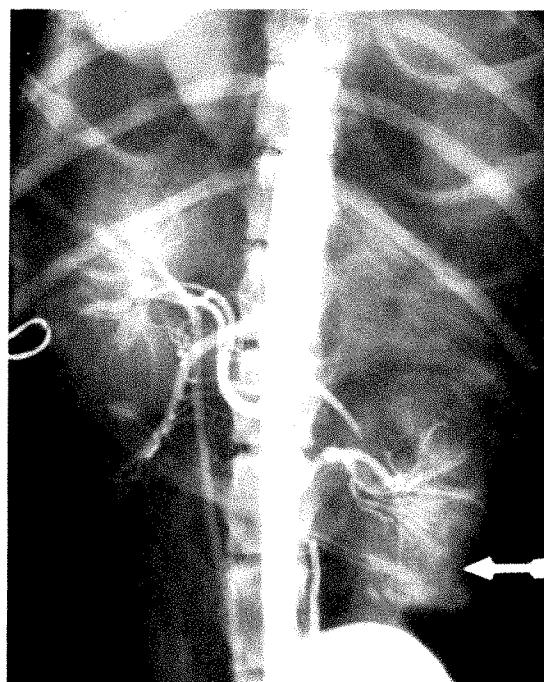


FIG. 9. Case III. Thirteen weeks post trauma; defects are still clearly seen in nephrogram phase. Healing has progressed as shown by haziness of margins.



FIG. 11. Case IV. Roentgenogram made in mid-arterial filling immediately following amputation of the lower pole of the left kidney. Note abrupt loss of vessels and extravasation of contrast material at site of amputation.



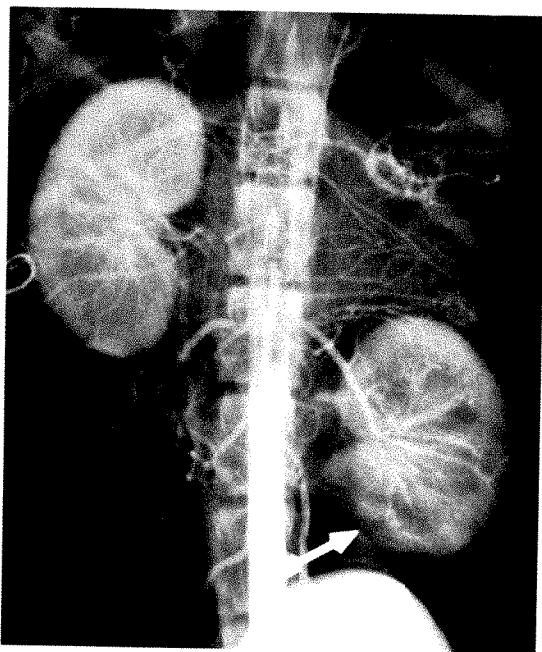


FIG. 12. Case iv. In the early nephrogram phase, the limits of the amputation are more clearly defined. Extravasation is less prominent.

from the amputated edge of the kidney can be demonstrated.

Finally, direct trauma to the renal artery was applied (Case vi, Fig. 17 and 18). The

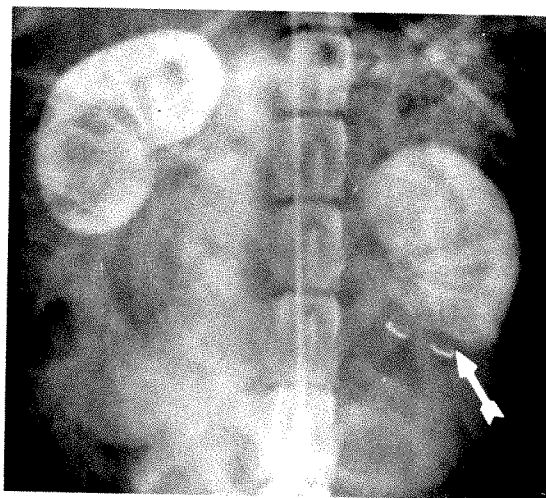


FIG. 14. Case v. In the nephrogram phase, the amputation borders are more clearly defined.

left renal artery was isolated and subjected to crushing by application of a hemostat many times over a specific segment. The arterial segment became discolored and contused. During retrograde catheter studies, definite areas of narrowing were seen at the site of trauma. One week and one month post trauma, abnormalities were still present.

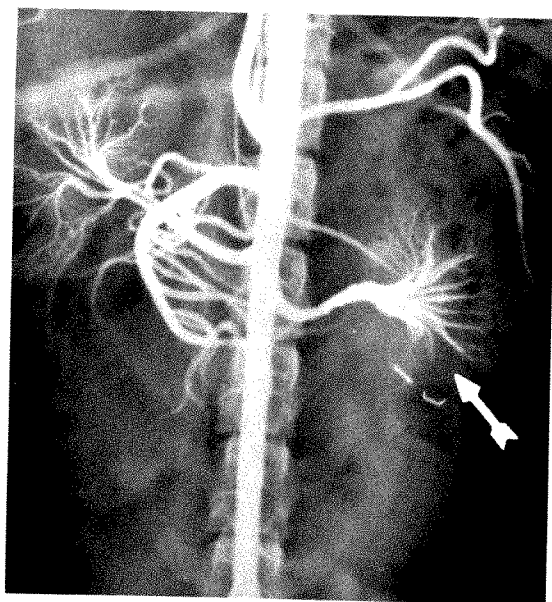


FIG. 13. Case v. Roentgenogram made in arterial phase following separation of lower pole of the left kidney and then replacement of lower pole by resuturing capsule. Note loss of vessel branches.

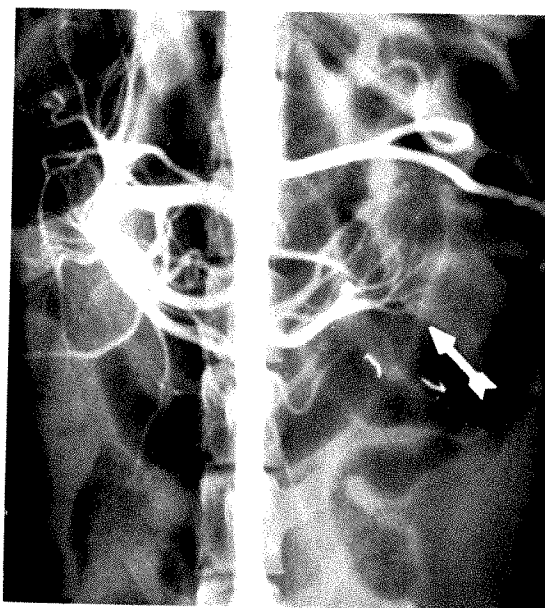


FIG. 15. Case v. One week following trauma, the loss of vessels appears to have spread more centrally than the edge of the amputation. This presumably is due to vessel thrombosis.

Following the initial trauma, the laparotomy was closed and all dogs were returned to the dog laboratory to await full recovery. They were then restudied at varying intervals. One week following trauma, early signs of healing were demonstrated. In the minimal lesion group, *i.e.*, those kidneys in which trauma could be demonstrated only in the nephrogram phase, no change was seen in the arterial pattern. However, in the nephrogram phase a definite haziness of the cleft defect developed. This group probably includes lesions up to 4 cm. in length.

In the group of more extensive lacerations, healing was more obvious as the lacerated edge developed a less well defined margin. In the group of kidneys with amputation of a lower pole tip, the defect was still seen by abrupt ending of arterial pattern and by a well defined loss of the nephrogram effect in the part of the kidney amputated. However, a definite change was noted in the healing process. A retrograde thrombosis of the arterial branches occurred so that the arterial vessel pattern appeared less peripheral than immediately

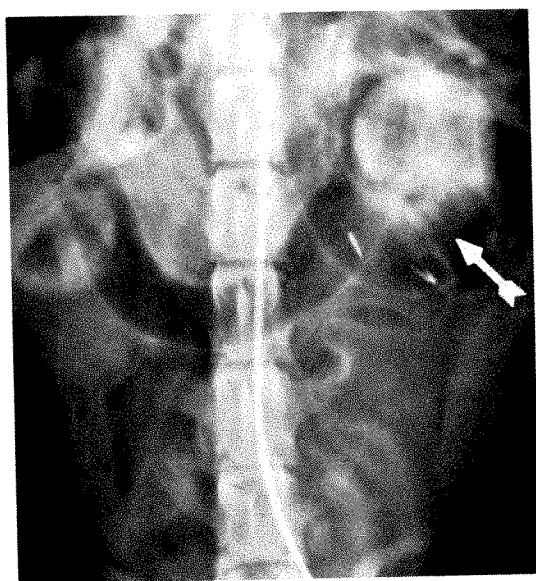


FIG. 16. Case v. Nephrogram effect shows loss of opacity along the edge of amputation and extending centrally as well.

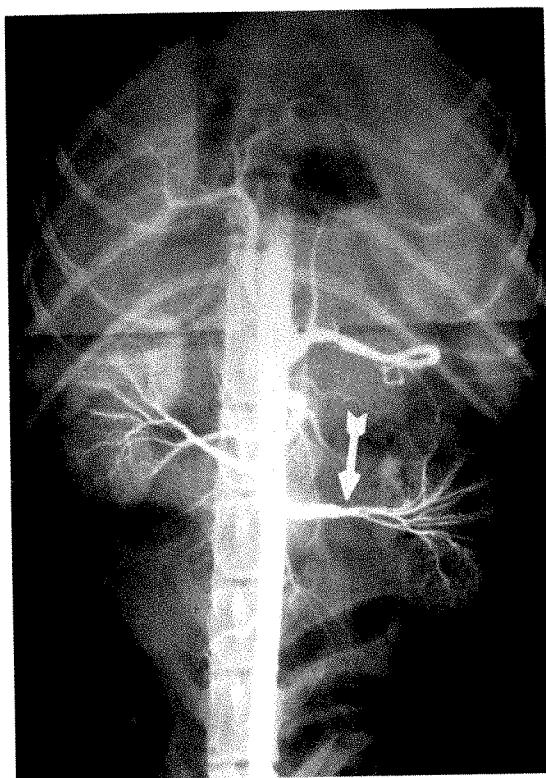


FIG. 17. Case vi. The left renal artery was isolated and subjected to crushing by application of a hemostat several times. The segment became discolored and appeared contused. Roentgenogram following trauma shows irregular narrowed areas.

post trauma. The nephrogram phase also decreased away from the line of amputation to coincide with the retrograde thrombosis.

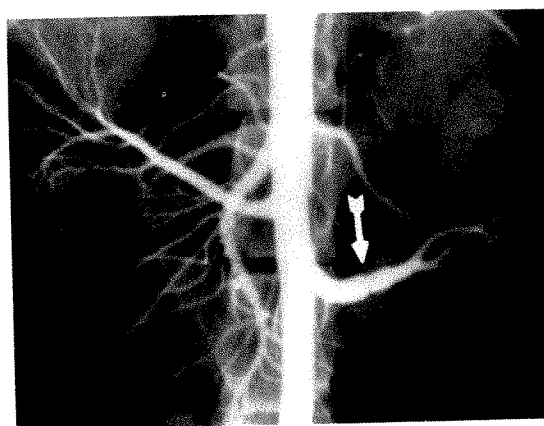


FIG. 18. Case vi. Study 1 week post trauma shows narrowed areas still present at site of trauma.

SUMMARY

This work was performed to evaluate the degree of kidney trauma which could be reliably shown on retrograde renal arteriography. The Seldinger method of percutaneous retrograde catheterization was used. The material obtained suggests that small lacerations of the kidney will not be seen during the filling of the renal artery branches but can be seen in the nephrogram phase. The success of visualization will depend on the plane of injury in relationship to the roentgen-ray beam. Ideally, a cross sectional position of the lesion in respect to the roentgen-ray beam is needed. Study of potential kidney rupture in both anteroposterior and lateral views is thus suggested. Large amounts of overlying normal tissue will definitely obscure the small lacerations. Large lacerations will be best seen in nephrogram phase but are less dependent on the relationship of the plane of the lesion in respect to the roentgen-ray beam. Portions of the kidney traumatically amputated should be seen clearly in both arterial and nephrogram phases.

All animals were studied at intervals and signs of healing were demonstrated 7 days post trauma.

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THE ROENTGEN DIAGNOSIS OF RENAL VEIN THROMBOSIS*

EXPERIMENTAL ASPECTS

By ANDREW B. CRUMMY, M.D.,† and FLORENCIO A. HIPONA, M.D.‡

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RENAL vein thrombosis may occur as a complication of several diseases. In children it is often related to dehydration secondary to diarrhea.² Such diverse pre-existing pathologic conditions as renal neoplasms, pyelonephritis, papillary necrosis, amyloidosis, trauma and inferior vena caval thrombosis have been reported in adults.^{1,9} The clinical picture of renal vein thrombosis, which depends to a great degree on the rapidity of the vascular occlusion, may be difficult to distinguish from the primary disease. If the thrombosis is rapid, the kidney becomes engorged, the capsule distends and hemorrhagic infarction results. In such instances, flank pain may be experienced and a tender, enlarged kidney may be palpated. However, if the venous occlusion is gradual, the renal engorgement may be minimal, pain absent and viability of the kidney is preserved.

Renal function may show only transitory derangement. The urinalysis frequently shows hematuria, albuminuria and pyuria. If involvement is unilateral and the kidney ceases to function, urinalysis may be normal. Some patients with bilateral or unilateral involvement may develop the nephrotic syndrome with hypertension, cholesterolemia and edema.⁷

In view of the nonspecific character of the clinical and laboratory manifestations of renal vein thrombosis, a roentgenologic study which would clarify the diagnosis is desirable. An experiment was undertaken to evaluate, by means of retrograde aortography and selective renal angiography, the response of the kidney to occlusion of

the renal vein, and to see if these procedures would be of value in the diagnosis of renal vein thrombosis.

COMPLETE OCCLUSION

Retrograde transfemoral aortorenal angiographies (Fig. 1, *A* and *B*) were performed on 5 dogs which had been anesthetized with nembutal.* The renal vein was then exposed and ligated close to the hilus. This was done on the right side in 3 dogs and on the left side in 2. The ligature on the left was proximal to the gonadal vein. Following completion of the surgery, angiography was repeated utilizing similar factors.

Inasmuch as thorotrast† is virtually not excreted by the kidneys,⁴ thorotrast was used as one of the angiographic contrast media to obtain an accurate delineation of the renal circulation: arterial, nephrographic and venous phases. For excretory urography, renografin-60‡ was employed as the contrast agent.

The kidney became rapidly tense and cyanotic. Postoperative angiographic studies showed the slowing of the flow of contrast material in the renal artery of the operated side, delayed appearance time in the renal veins, prolonged venous phase and the occluded renal vein. No collateral veins were visualized. The procedure was

* Nembutal Sodium: Trademark of Abbott Laboratories, North Chicago, Illinois, for pentobarbital sodium, U.S.P.

† Thorotrast: Trademark of Testagar & Co., Inc., Detroit, Michigan, for stabilized colloidal thorium dioxide solution.

‡ Renografin-60: Trademark of E. R. Squibb and Sons, New York, New York, for diatrizoate methylglucamine injection, U.S.P.

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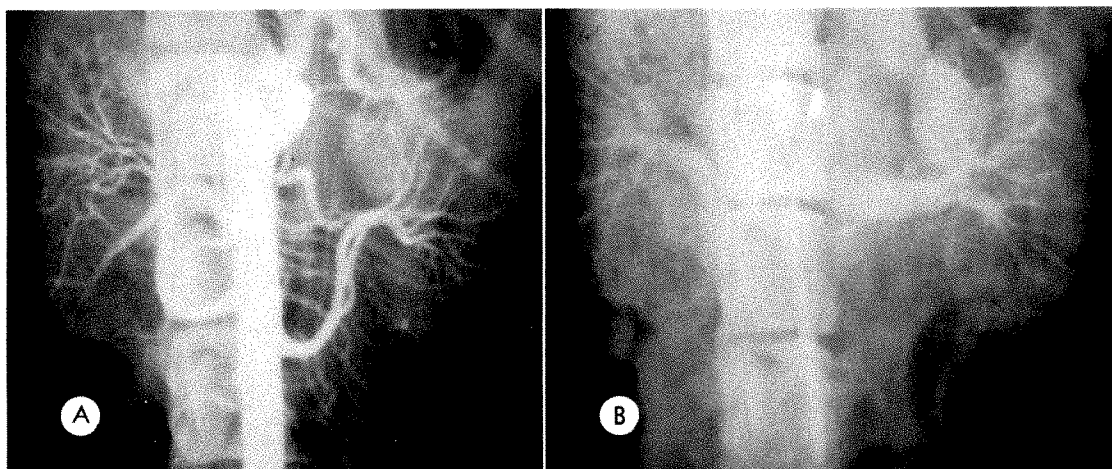


FIG. 1. (A and B) Control retrograde aortograms demonstrated normal renal arteries, symmetric nephrograms and simultaneous opacification of the renal veins at 3 seconds.

found to be uniformly fatal within 18 hours. Necropsy showed rupture of the kidney and retroperitoneal hemorrhage.

PARTIAL OCCLUSION

In a second group of dogs, the above experiment was repeated but partial, rather than complete, occlusion of the renal vein was produced. This procedure was done on the right side in 2 animals and in 2 other animals on the left side. The caliber of the vein was reduced to an estimated 75 per cent. Serial studies by retrograde aortography, selective renal angiography and excretory urography were done preoperatively, in the immediate postoperative period and subsequently at varying intervals. At the end of 8 weeks, the animals were sacrificed and vinylite corrosion casts of the retroperitoneal venous system and upper urinary tract were made *in situ*.

Immediately following partial venous occlusion, the kidney became turgid and dusky but the changes were not as marked as in the cases of total occlusion. The angiogram made within 30 minutes of the partial occlusion showed that kidney size began to increase immediately. The maximum increase in size, judged by the length of the horizontal and vertical axes, occurred about the third postoperative day. Serial studies during the 8 week period showed gradual

reduction in kidney size which stabilized at about 25 per cent larger than the control value.

On the side of the partial occlusion, the arterial phase was initially prolonged and the caliber of the arteries was reduced. The intraparenchymal vessels were spread and many of the small vessels were not visualized. The over-all appearance was similar to that seen in moderate hydronephrosis. The origin of the renal artery from the aorta remained unchanged in size. However, the caliber tapered and reached a minimum diameter between 0.5 and 1.0 cm. from the aorta. The over-all appearance of the proximal renal artery was much like that of an arrowhead (Fig. 2, A, B and C). The nephrographic phase was less dense.

As the size of the kidney began to decrease, the renal artery caliber increased as did the intensity of the nephrogram. When these findings had stabilized, the small intraparenchymal vessels were better seen but not as well as on the preoperative angiogram. These changes would allow one to infer that renal blood flow was reduced.

The reduction in renal size, the return of renal blood flow and caliber of the renal artery toward normal closely paralleled the development of an extensive venous collateral circulation. As early as the fifth postoperative day, venous collaterals were

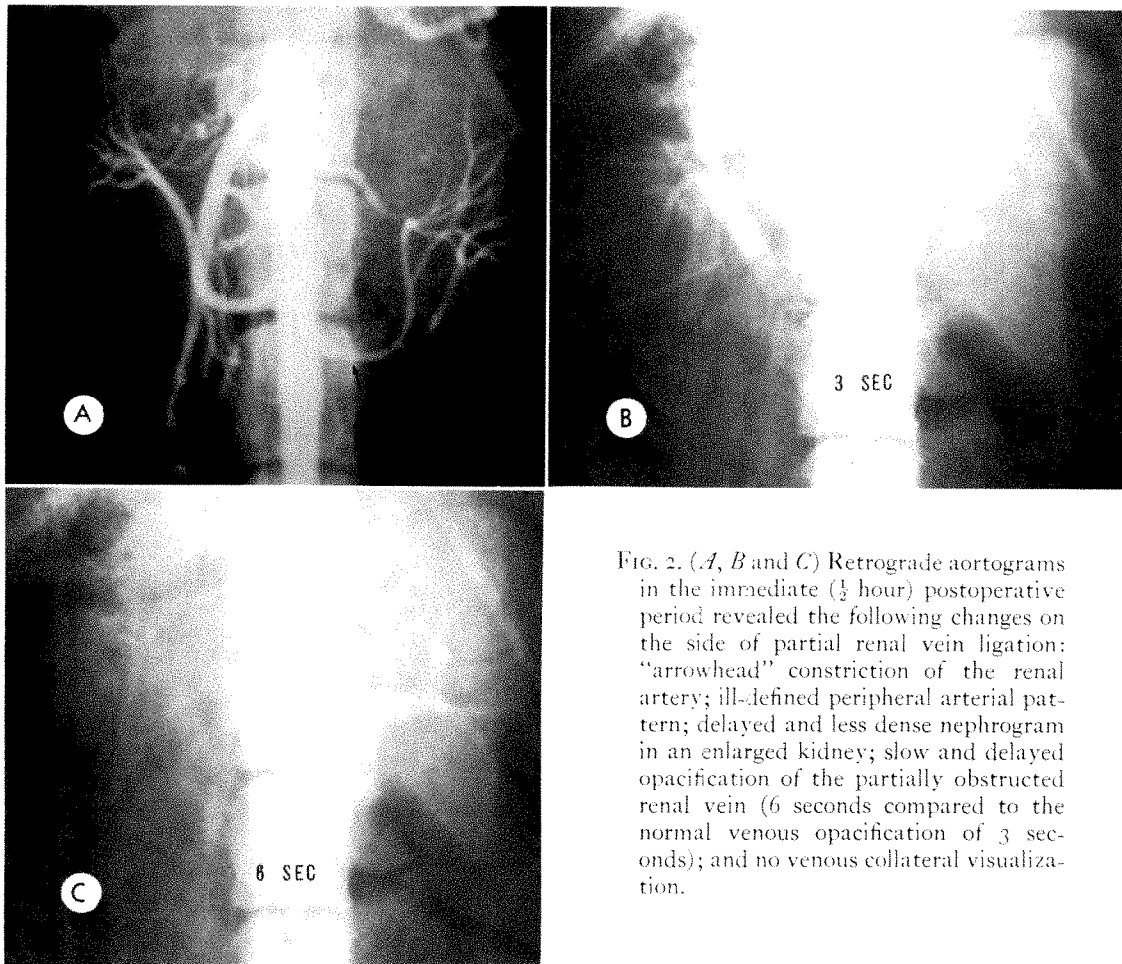
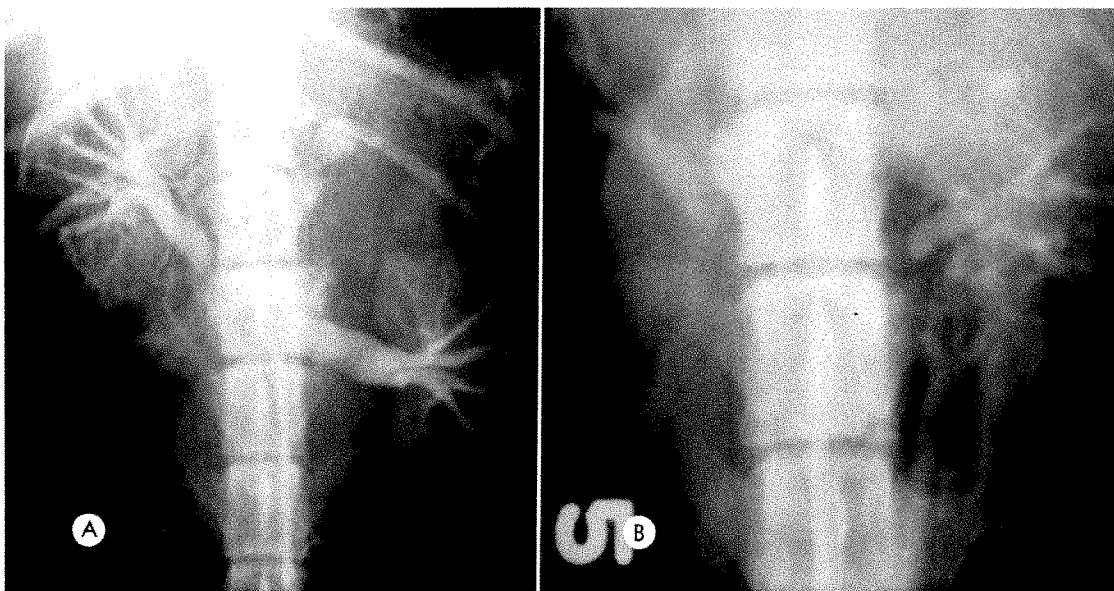


FIG. 2. (*A, B and C*) Retrograde aortograms in the immediate ($\frac{1}{2}$ hour) postoperative period revealed the following changes on the side of partial renal vein ligation: "arrowhead" constriction of the renal artery; ill-defined peripheral arterial pattern; delayed and less dense nephrogram in an enlarged kidney; slow and delayed opacification of the partially obstructed renal vein (6 seconds compared to the normal venous opacification of 3 seconds); and no venous collateral visualization.



detectable and optimum demonstration was present by the twelfth day. Selective renal artery injection provided the best means of opacification of veins draining the kidney and proved conclusively that the vessels were not filling from other viscera frequently seen in retrograde aortograms.

Most of the angiographically demonstrable collaterals (Fig. 3, *A* and *B*) were part of the ureteric plexus of veins. Ordinarily, the ureteric venous network is very small and does not opacify. The direction of blood flow in the ureteric vein is obscure, but the blood from the upper third of the ureter is believed to drain towards the renal vein.^{6,8} Under circumstances such as renal vein occlusion, the ureteric vein enlarges and drains part of the renal blood into the vesical plexus which connects with the internal iliac vein. This anastomosis was well delineated by internal iliac vein injection of contrast material after balloon obstruction of the inferior vena cava (Fig. 4).

The ureteric vein was one of the two major collateral systems which were observed by Hollinshead and McFarlane,⁵ and Cox *et al.*³ in their dissections following partial renal vein occlusion. The other major system is the subcapsular plexus of veins which was discernible in one of our angiograms. These veins drained into the perirenal veins and then into the adrenal, gonadal and lumbar group which intercommunicate with the ureteric venous plexus.

Renal function was grossly assessed by means of intravenous urography. All the kidneys continued to excrete the contrast and no difference in concentration was detectable. The ureter on the side of the occlusion showed a scalloping-type defect (Fig. 5).

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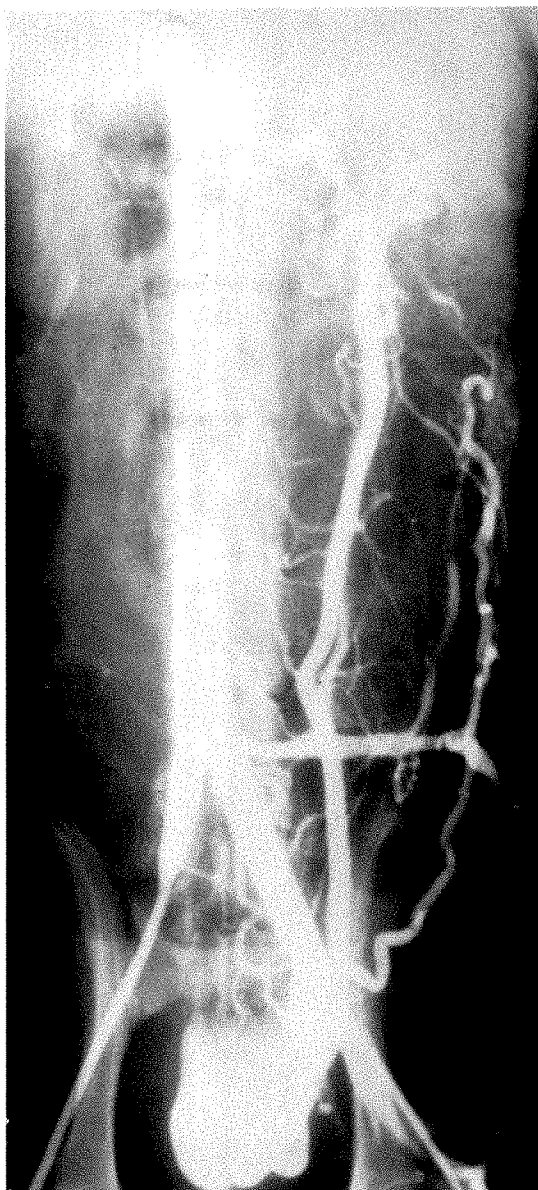


FIG. 4. Selective injection of radiopaque contrast medium into the left internal iliac vein with simultaneous balloon obstruction of the proximal inferior vena cava. This study demonstrated opacification of the ureteric vein which intercommunicated with the ovarian, lumbar, capsular and adrenal veins.



FIG. 3. (*A* and *B*) Aortorenal angiograms showed return of arterial, nephrographic and venographic circulation to almost normal. However, there was additional opacification of venous collaterals. Ureteric and capsular veins seen in (*A*) right sided lesion, 20 days postoperatively, in (*B*) left sided lesion, 7 days postoperatively.



FIG. 5. Excretory urogram showed scalloping effect on the proximal left ureter due to the dilated ureteric vein.

corrosion casts of the venous system of the retroperitoneal space and the upper urinary tract were made.¹⁰ By this method, the well developed collateral system was demonstrated and confirmed the angiographic ob-

servations (Fig. 6, *A* and *B*). The subcapsular plexus was better outlined. The close relationship of the dilated and tortuous ureteric vein with the ureter was demonstrated. The undulations of the ureter were confirmed to be secondary to extrinsic pressure from the distended ureteric varices.

SUMMARY

The response of the dog kidney to acute complete and acute partial obstruction of the renal vein was studied by means of angiography. The capability of the kidney to survive renal vein obstruction depends upon the rapid development of an adequate collateral venous drainage. The appearance of the kidney and the renal circulation undergo rapid change and reflect the development of the collateral venous drainage.

On the basis of experimental results, renal angiography is an excellent method of investigating renal vein thrombosis. Exami-

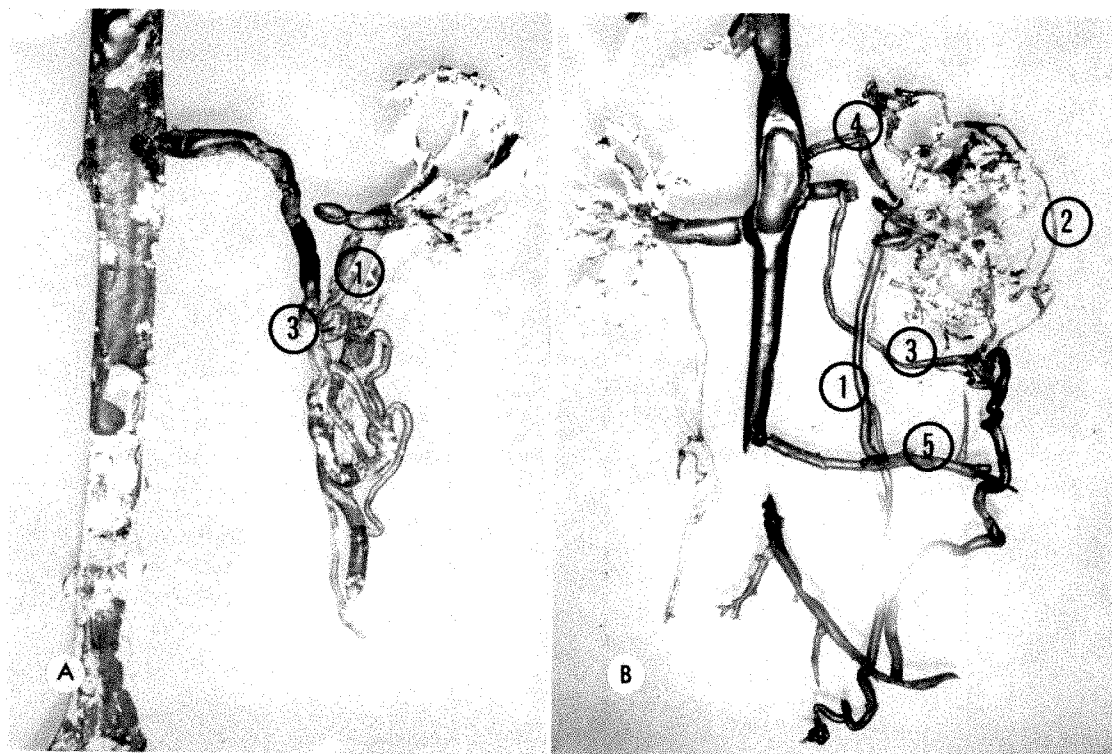


FIG. 6. (*A* and *B*) Vinylite corrosion casts of the retroperitoneal venous system and the upper urinary tract. The roentgenographic findings were confirmed and demonstrated the following venous collaterals: (1) ureteric vein; (2) capsular venous network; (3) ovarian vein; (4) adrenal vein; and (5) lumbar vein.

nation will show the arteriographic, nephrographic and venographic effects of thrombosis of the renal vein. Furthermore, the study may show the pattern of vascular flow in the collateral circulation.

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ANGIOGRAPHIC STUDY OF THE EFFECT OF VASOPRESSORS—EPINEPHRINE AND LEVARTERENOL—ON RENAL VASCULARITY*

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ABRAMS *et al.*¹ demonstrated clearly the feasibility of the use of angiography to study the effect of epinephrine on the renal circulation. With aortography or selective renal angiography in the dog, they showed that epinephrine in intravenous doses of 10 to 40 μ g. per kg. produces a zone of marked local narrowing at or near the bifurcation of the renal artery with dilatation of the artery proximal to this "sphincteric" constriction.

Later, Abrams² injected epinephrine into the renal artery of a patient with hypernephroma of the kidney, in a dose of 0.25 μ g. per kg. This was followed by selective renal angiography 50 seconds after the administration of the epinephrine. There was opacification of tumor vessels but not of the normal parenchymal vessels, indicating that neoplastic vessels differ from normal vessels in their response to epinephrine. He suggested that at this low dose the major effect of epinephrine is probably on the arteriolar bed as contrasted to the effect of the larger doses in the dog on the main renal artery.

There is general agreement that vasopressors cause an increase in renal vascular resistance with a subsequent decrease in the renal blood flow. However, agreement is not general as to the site or sites of the increased resistance. Epinephrine has been the subject of much study in this respect.

Richards and Plant¹⁷ reported that epinephrine causes constriction of the efferent arterioles, resulting in an increase in intraglomerular pressure and distention of the glomeruli as well as swelling of the kidney; they perfused the isolated dog or

rabbit kidney with addition of a small amount of epinephrine to the perfusate. Worthen *et al.*²⁶ reported that epinephrine causes constriction of the afferent arterioles with no increase in kidney weight; they perfused isolated dog kidneys at constant pressure, measuring changes in blood flow, urine flow, arterial and intrarenal venous pressures, and renal volume after single injections of synthetic epinephrine in small doses (*e.g.*, 0.001 μ g. per injection). Winton²⁴ stated that there is constriction of the efferent arterioles and dilatation of the afferent arterioles; he also had perfused dog kidneys at a constant arterial pressure. Moyer and Handley¹⁶ reported that epinephrine and norepinephrine reduce renal blood flow by producing efferent arteriolar vasoconstriction. Smith *et al.*²⁰ held that the efferent glomerular arterioles afford the primary intrinsic regulation of the renal blood flow in man. They observed that the filtration rate remains essentially unchanged during epinephrine-produced diminution in the renal blood flow. Later, Maxwell and his group¹³ reported that in man epinephrine (within the usual therapeutic dose range) increases all segmental renal resistance, although the effect is greatest in the venular resistance.

Mehrizi and Hamilton¹⁴ reported that levarterenol produces increased resistance in the postcapillary segments, resulting in diminished renal blood flow, renal swelling, distention of the glomerular and possibly of the peritubular capillaries. They used a dye dilution method in anesthetized dogs to calculate renal blood flow and mean transit time.

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The disparities in the reported actions of a given vasopressor on the kidney might be due to differences in the experimental set-up (such as isolated kidney as compared to those in the intact animal) or differences in dosage. Similar considerations might apply to the differences in the site of action attributed to various vasopressors, or the vasopressors may actually not be similar in action. Physiologic yardsticks used to deduce mechanisms of actions of the vasopressors in respect to the kidney have included measurement of: clearances, filtration fraction, urine output and renal volume. Visualization of the larger renal artery branches by angiography has yielded significant findings. Trueta *et al.*²¹ carried out aortography in the rabbit using sodium iodide and thorotrast; epinephrine in high dosage (100 to 170 μ g. per kg.) administered intravenously produced narrowing of the renal arteries and renal veins.

Voudoukis and Boucek²² observed the effects of several vasopressors by performing aortography in the anesthetized dog, obtaining single roentgenograms of renal vessel filling at a predetermined and selected phase of the cardiac cycle (intercalative angiography). They concluded that pharmacologically induced vasoconstriction in the kidney is mediated by 2 types of responses: (a) constriction of the lobular and cortical arterial branches, and (b) a generalized response affecting all of the renal artery branches. Epinephrine and norepinephrine in small doses produced response (a) and in larger doses response (b). Unfortunately, exact dosages were not stated nor was mention made of the contrast medium used. It appears that "small doses" refer to about 6 μ g. per kg. for epinephrine.

For determination of renal blood flow, methods employing clearance studies, such as the clearance of diodrast or para-aminohippuric acid, are not applicable or reliable in situations where urine flow is greatly diminished or where urine samples cannot be collected. Clearance methods do not detail rapidly changing and short periods

of blood flow variation. Also, clearance methods prove inaccurate in the presence of rapid changes in systemic blood pressure. Methods requiring operative attack on the renal vessels, such as rotameters, thermistomuhrs, electromagnetic flowmeters and bleeding from the renal vein, are not satisfactory because of the possible abnormalities produced by the operation itself. Various dilution methods—dye, thermal or tagged albumen—are under study and may prove useful. Other possibilities include the gas diffusion technique and the disappearance rate of radioactive krypton with which the renal tissue has been saturated.

Roentgenologic methods employing selective angiography can reveal a good deal about the anatomy of renal vascularity and also provide important information about changes in blood distribution in the kidney without accurately quantitating the flow. Yet it may be possible with refinements in technique and evaluation to develop the method of selective angiography as a useful determinant of blood flow.⁶

In an attempt to define further the effect of vasopressor drugs on renal vascularity, a series of studies has been done with various doses of epinephrine (suprarenin) and levarterenol (norepinephrine). In addition to determining the results of different dose levels, there was also interest in the relative effectiveness of these two drugs on the renal vessels as well as in the investigation of the mechanism of their action.

TECHNIQUE

Our studies have been done on dogs weighing 12 to 20 kg. A preshaped catheter (Ödman red with an external diameter of 2.0 mm. and a lumen diameter of 1.15 mm.) was inserted percutaneously into the femoral artery using the Seldinger technique. Under fluoroscopic control, the tip of the radiopaque catheter was guided up the aorta into the orifice of one of the renal arteries. In order to approach reproducibility of injection factors in serial angiography, an automatic injector (Cordis) was used, which not only injects the same

amount of contrast medium each time at the same pressure, but also initiates the roentgenographic exposure at the same time in the course of the injection. Inasmuch as the intrarenal veins are partially obscured by renal opacification produced by contrast medium excreted by the kidney, most of the studies were done with thorotrast, which is not excreted in the urine. The dose of thorotrast was 0.2 cc. or 0.3 cc. per kg. Roentgenograms were made at the speed of 2 per second. Also cine-fluorography has been done at speeds of 16, 32 or 64 frames per second. Blood pressure was continuously monitored by a catheter in the opposite femoral artery, using a pressure transducer. Also, aortography has been performed with the tip of the catheter in the aorta using hypaque (50 per cent) or thorotrast in dosage of 1 cc. per kg.

In attempting to develop selective renal angiography as a rough measure of blood flow the following phenomena have been noted and evaluated:

1. Size of the main renal artery.
2. Degree of reflux of contrast medium into the aorta.
3. Size of the interlobar arteries.
4. Tortuosity of the interlobar arteries.
5. Speed of emptying of the main renal artery and its branches.
6. Intensity of the nephrogram.
7. Extent and regularity of the zone of cortical intensification.
8. Rapidity with which the intrarenal veins are first opacified.
9. Opacified size of the renal vein and its major feeding branches.
10. Rapidity of emptying of the intrarenal veins and the main renal vein.
11. Size of the kidney.

In our dogs the main renal artery measured about 4 mm. in diameter, gradually tapering in size to its major branches and then to the interlobar arteries. Discrete arcuate arteries and interlobular arteries were not usually seen, although the rich cortical flow was manifest by intense cortical opacification during the nephrographic

phase, the cortical rim measuring about mm. to 8 mm. in width with well defined margins. With thorotrast there was good opacification of the main renal vein, major branches and the interlobar vein. There was usually no or only very little reflux of the contrast medium into the aorta under normal conditions during selective study. The arteries were empty of opaque medium in $1\frac{1}{2}$ to 2 seconds with first opacification of the intrarenal veins second later. By 5 seconds the veins were no longer opacified or only partially opacified.

Single dose intravenous administration of the tested drug was used for the main part, although long period intravenous infusion was employed in a few experiments. In the case of single dose injection, drug was diluted with saline to a constant volume (5 cc.) and angiography was performed at the height of the blood pressure response—45 to 60 seconds after completion of the injection for epinephrine and arterenol. Initially, repeated experiments showed that the contrast media used in these studies do not, in themselves, cause a change in the appearance of the angiogram. It was also demonstrated that presence of the catheter in the renal artery does not change the appearance of the renal blood vessels (Fig. 1, *A* and *B*).

EPINEPHRINE

Doses of 0.5 to 1.0 μ g. of epinephrine/kg. usually caused no perceptible change in the angiogram, although in an occasional animal there was slight prolongation of vascular phases. These doses produced only a slight rise in the mean systemic blood pressure, usually less than 10 mm. and sometimes no rise at all.

With 2 to 5 μ g. per kg. there was an increase in the caliber of the main renal artery and its major branches as well as dilatation of the interlobar arteries. In some experiments the nephrogram showed loss of intensity, the vascular phases were not changed in timing, the veins filled as well as in the control angiogram and the kidney did not change in size. In such experiments

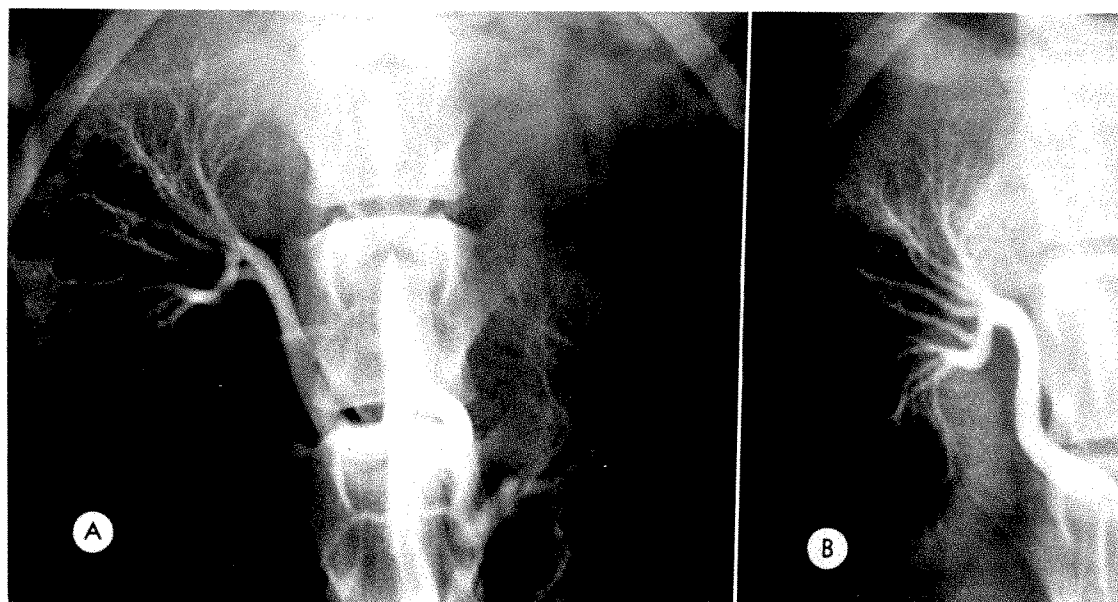


FIG. 1. (A) Thorotrast aortogram, with catheter in the aorta, demonstrates renal arterial distribution. (B) Thorotrast selective right renal angiogram of same dog as in A shows the arteries of the kidney to appear unchanged.

the angiograms suggested no perceptible change in the renal blood flow. In view of the increased mean blood pressure at the time of the post-epinephrine angiogram—about 40 mm. Hg with the 2 μ g. dose and 75 mm. Hg with the 5 μ g. dose—the lack of changes suggesting increased flow indicates increased renal resistance, very likely peripheral to the interlobar arteries resulting in the dilatation of main renal and interlobar arteries. In several dogs this dose caused diminished intensity of the nephrogram and prolongation of the vascular phases, indicating a diminution in blood flow in spite of normal or increased caliber of the main and interlobar arteries (Fig. 2, A and B; and 3, A and B). Again, these findings in conjunction with diminished cortical intensification during the nephrographic phase indicated increased vascular resistance peripherally in the kidney.

With large doses of epinephrine, 15 to 60 μ g. per kg., there was evidence of marked increase in renal vascular resistance, our findings confirming those reported by Abrams *et al.*¹ With the rise in mean blood pressure—about 145 mm. Hg with the 30 μ g. dose—there was dilatation of the aorta, lumbar arteries, mesenteric arteries and the

main renal arteries. However, the major branches of the renal artery showed narrowing near the site of branching of the main renal artery; this constriction was sudden and marked, its extent dependent somewhat on the dose of epinephrine used. There was poor filling of the interlobar arteries which were narrowed, and marked diminution or absence of the vascular nephrogram (Fig. 4, A, B and C). Intrarenal veins and the main renal vein were poorly filled, late in being visualized if at all, and, when seen, appeared smaller in caliber than in the control study. As further evidence of the increased renal vascular resistance, there was on selective studies marked reflux of the opaque medium from the renal artery into the aorta.

LEVARTERENOL (NOREPINEPHRINE, LEVOPHED)

Ahlquist *et al.*³ reported that levarterenol has a greater pressor action than epinephrine, but causes less intense renal vasoconstriction than does epinephrine. Goodman and Gilman⁸ stated that levarterenol is 1½ times more active than epinephrine in respect to pressor activity. The method used in our levarterenol studies was similar to those with epinephrine, allowing a com-

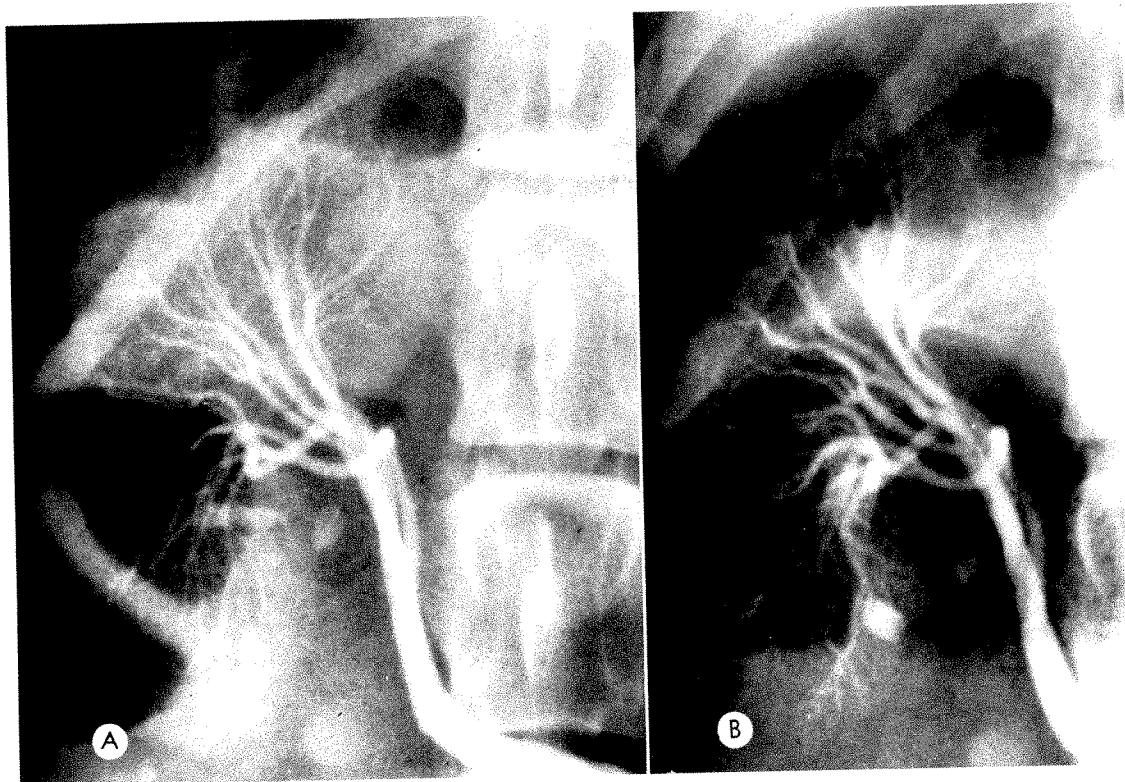


FIG. 2. (A) Control thorotrast angiogram, 1 second after injection of the thorotrast (1 second film). (B) Thorotrast angiogram after intravenous epinephrine, 2 $\mu\text{g.}/\text{kg.}$ (1 second film). Slight increase in caliber of main renal artery and more pronounced increase in size of the interlobar arteries.

parison of the two drugs. The results indicated that levarterenol is actually as potent as or possibly more so than epinephrine in respect to effects on the renal vascularity. Inasmuch as the two molecules are of about the same size (molecular weight of levarterenol about 8 per cent less than that of epinephrine), a comparison of the dosage of the two compounds by weight administered rather than moles equivalent is sufficiently accurate.

A dose of 0.5 to 1.0 $\mu\text{g.}$ of levarterenol per kg. usually showed slowing of the vascular phases and diminution in the intensity of the nephrogram with slight increase in the caliber of the main renal artery. Hence, even at this small dose, there was indication of increased vascular resistance. With the 0.5 $\mu\text{g.}$ dose, the mean systemic blood pressure rose about 30 mm. Hg.

At a dose of 5 $\mu\text{g.}$ per kg. levarterenol produced in most experiments slight constriction of the major renal artery branches

near the point of branching of the main artery with diminution in size of the interlobar arteries, lessening of the intensity of the nephrogram and late and poor filling of the intrarenal veins (Fig. 5, A-F). These changes indicate increased resistance at the level of the major renal arteries, whereas this dose of epinephrine had produced changes indicating increased resistance peripheral to the interlobar arteries.

The larger doses of levarterenol—15 to 60 $\mu\text{g.}$ per kg.—showed changes like those produced by similar doses of epinephrine, usually with marked constriction at or just beyond the bifurcation of the main renal artery with narrowed interlobar arteries and diminished nephrogram (Fig. 6, A and B).

With both epinephrine and levarterenol at all tested doses, the kidney, where measurable, usually showed no change in size as seen on the roentgenogram. In only a few experiments, the kidney diminished

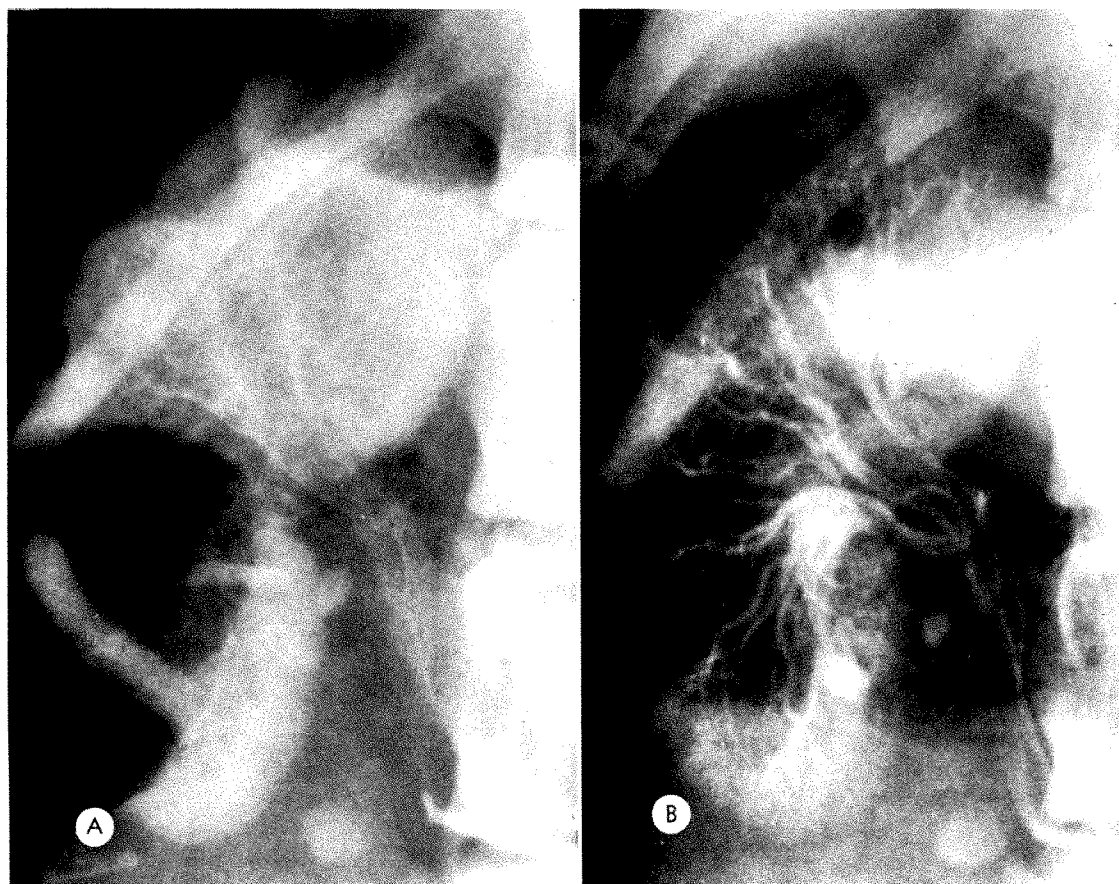


FIG. 3. (A) Control angiogram, 0.5 second after 2A, shows nephrogram phase with the arteries almost completely emptied of opacified blood. (B) Postepinephrine angiogram, 0.5 second after 2B, shows the arteries still opacified, indicating prolongation of the arterial phase as compared to 3A.

slightly in size with either drug in dosage of 5 μ g. per kg. or higher. In no case was an increase in size of the kidney noted.

MECHANISM OF ACTION

Are the renal vascular changes in response to the systemic hypertension produced by the epinephrine and the levarterenol or is there a direct action of these drugs on renal vessels? The increased renal vascular resistance could be a manifestation of autoregulation, representing one of the physiologic alterations which allow the kidney to maintain a relatively constant blood flow despite changes in blood pressure. Except for a few investigators,^{5,11} most workers agree that the kidney does manifest autoregulation.^{7,9,10,18,19,25} The proponents of the autoregulation theory

state that with a rise in blood pressure (the perfusing pressure) the renal blood flow is kept relatively constant by an increase in the renal vascular resistance. The suggested sites of increased resistance include post-glomerular segments (efferent arteriolar and venous) with fall in pre-glomerular resistance,¹⁰ afferent arterioles,^{7,18} and venous segments.²⁵

Ahlquist *et al.*,³ Langston *et al.*,¹² and Aviado *et al.*⁴ reported direct effect of these drugs on the renal vessels.

In several experiments epinephrine was mixed directly with the thorotrast, this mixture being injected under the same conditions as with control angiography. Amounts of 7.5 μ g. of epinephrine per kg. when mixed with the thorotrast produced no perceptible changes except possibly

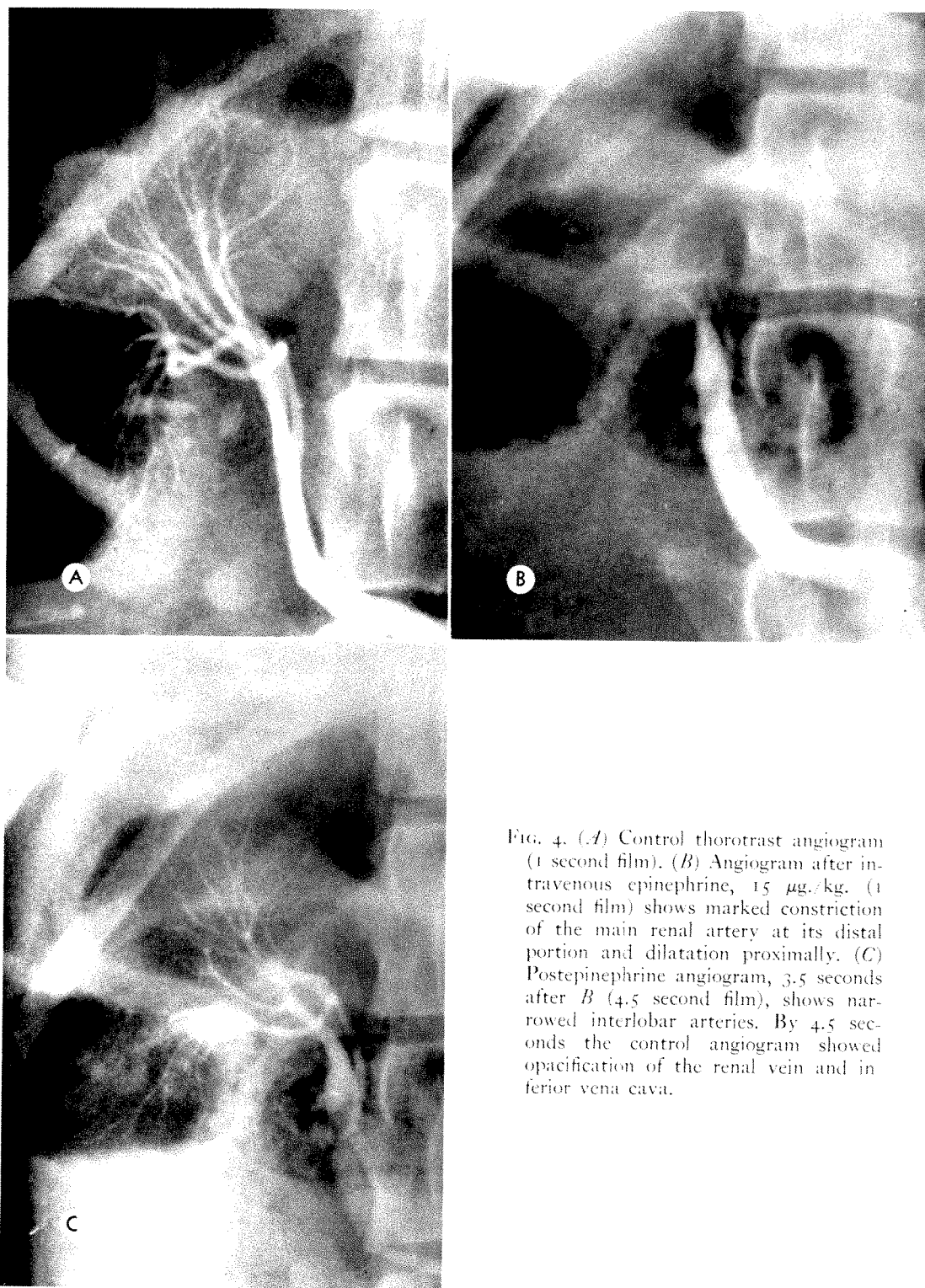


FIG. 4. (A) Control thorotrast angiogram (1 second film). (B) Angiogram after intravenous epinephrine, 15 $\mu\text{g.}/\text{kg.}$ (1 second film) shows marked constriction of the main renal artery at its distal portion and dilatation proximally. (C) Postepinephrine angiogram, 3.5 seconds after B (4.5 second film), shows narrowed interlobar arteries. By 4.5 seconds the control angiogram showed opacification of the renal vein and inferior vena cava.

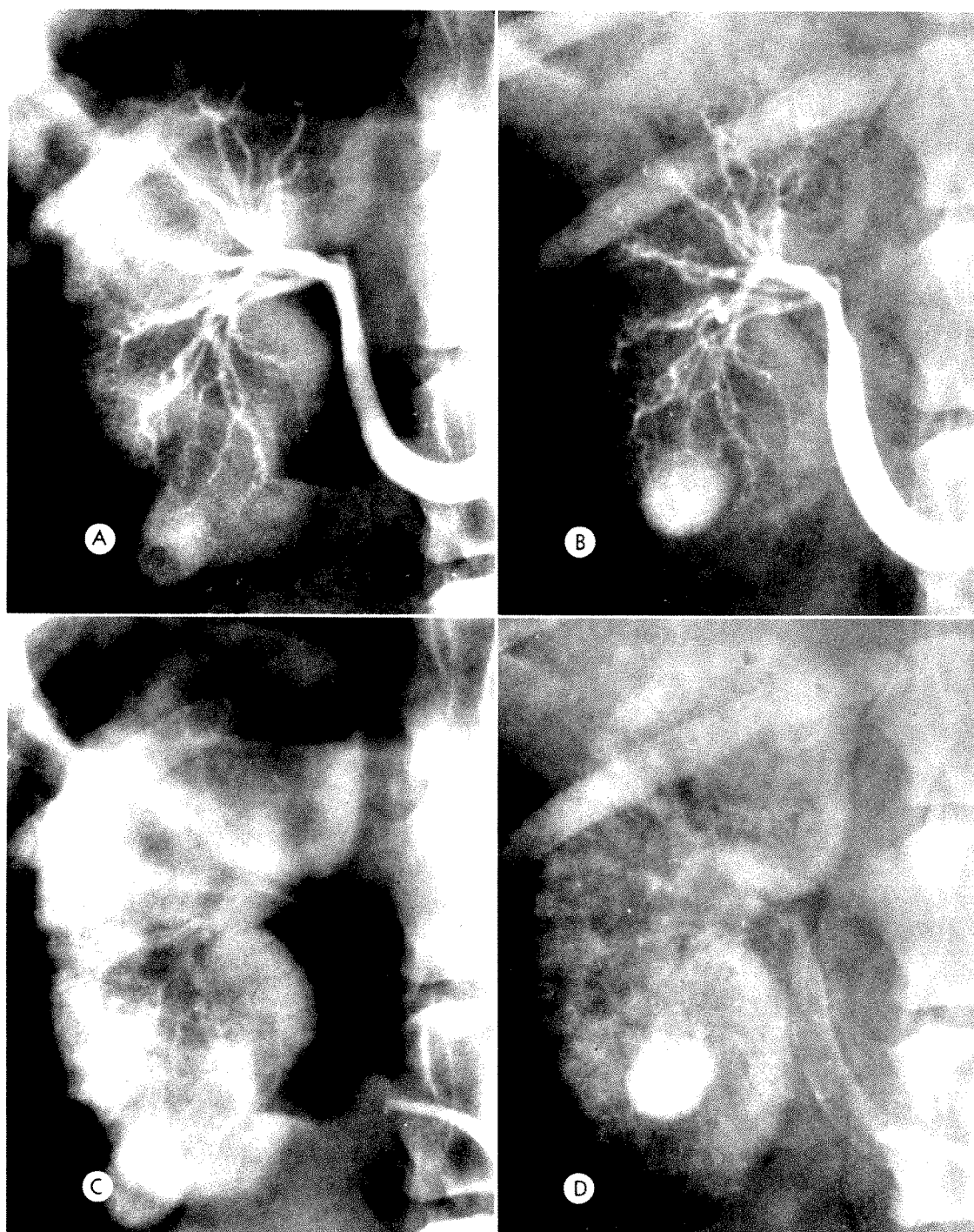


FIG. 5. (A) Control thorotrast angiogram (1 second film). (B) Thorotrast angiogram after intravenous levarterenol, 5 $\mu\text{g.}/\text{kg.}$, (1 second film) shows constriction of the distal main renal artery with dilatation proximally. The interlobar arteries are narrowed and tortuous. (C) Control angiogram (1.5 second film) shows a good nephrogram. (D) Postlevarterenol angiogram, 1 second after B (2 second film), shows the nephrogram to be later in appearance and less in intensity than in the control (C).

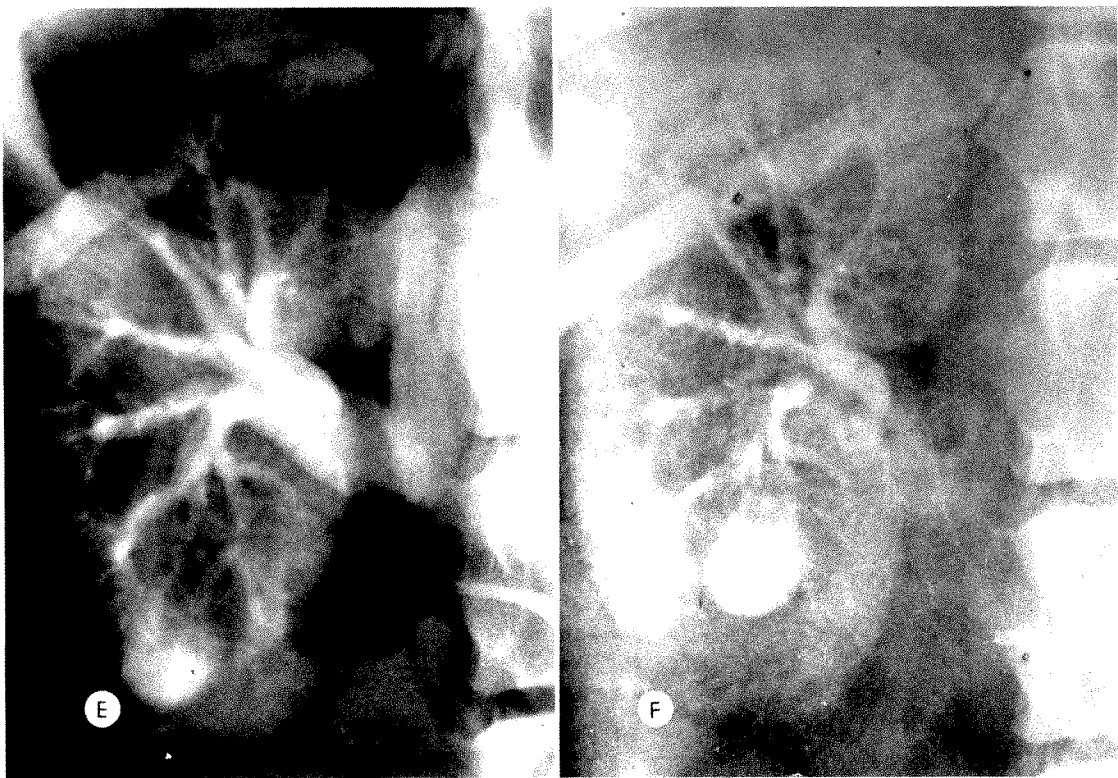


FIG. 5. (E) Control angiogram (3 second film) shows good opacification of the intrarenal veins, main renal vein and inferior vena cava. (F) Postlevarterenol angiogram, 1 second after D (3 second film), shows poor opacification of the renal veins.

for slight dilatation of the main renal artery; 30 μ g. per kg. mixed with the thorotrast produced enlargement of the

main renal artery and of the interlobar arteries, as well as marked slowing of the arterial phase. In these experiments angi-

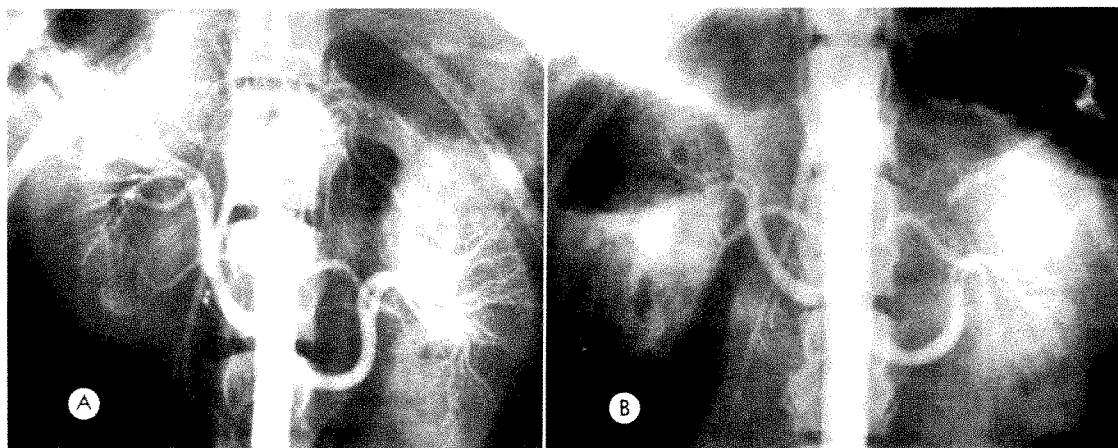


FIG. 6. (A) Control thorotrast aortogram (1 second film). (B) Thorotrast aortogram after intravenous levarterenol, 45 μ g./kg., (1 second film) shows dilatation of aorta, lumbar arteries and proximal main renal arteries. There is marked constriction just beyond the bifurcation of the main renal arteries with narrowed interlobar arteries.

ography had been completed before the occurrence of the blood pressure rise. These studies indicate that epinephrine does have a direct action on the renal vascularity although its full effect could very likely not be demonstrated by this method in which the epinephrine and contrast medium reach the vessels simultaneously.

A catheter was inserted percutaneously into each femoral artery and guided retrograde in the aorta so that both renal arteries were catheterized. Control angiography was done with thorotrast (0.5 cc. per kg.), the medium being injected by the automatic injector at the same time into both catheters through a Y-connector. Then epinephrine was injected into the catheter to the right kidney (30 μ g. per kg.) followed immediately by thorotrast into both catheters through the Y-connector. On the right side there was dilatation of the proximal part of the main renal artery with marked constriction just proximal to its bifurcation with no filling of the interlobar arteries. The angiogram on the left side appeared normal (like the control) (Fig. 7, *A* and *B*).

As further evidence of a direct effect of epinephrine on the renal vessels is the difference in the appearance of the angiograms on the two sides in "recovery" studies. Epinephrine—30 μ g. per kg.—was made up

to 1 cc. with saline and injected rapidly into the right renal artery, followed immediately by angiography. During the time of angiography there had been only slight systemic blood pressure change (elevation of 9 mm. Hg) with the major blood pressure elevation beginning about 10 seconds and its peak 27 seconds after completion of angiography (elevation of 60 mm. Hg). The renal artery showed marked constriction at its bifurcation with no opacification of the interlobar arteries. Then a bilateral selective study done 35 minutes after the epinephrine injection showed a marked difference in the appearance of the two sides. On the right there was still some constriction at the distal main renal artery with dilatation of its proximal part, slow filling of the intrarenal arteries, no nephrogram and no venous filling in 5 seconds. On the left side the intrarenal arteries appeared normal with fairly normal vascular phases.

Bilateral selective renal angiograms similarly demonstrated a direct effect of levarterenol. Forty-five micrograms per kg. injected into the left renal artery showed marked constriction of the artery just beyond its bifurcation with only slight opacification of the interlobar arteries which appeared attenuated. The angiogram of the right side remained like the control (Fig. 8,

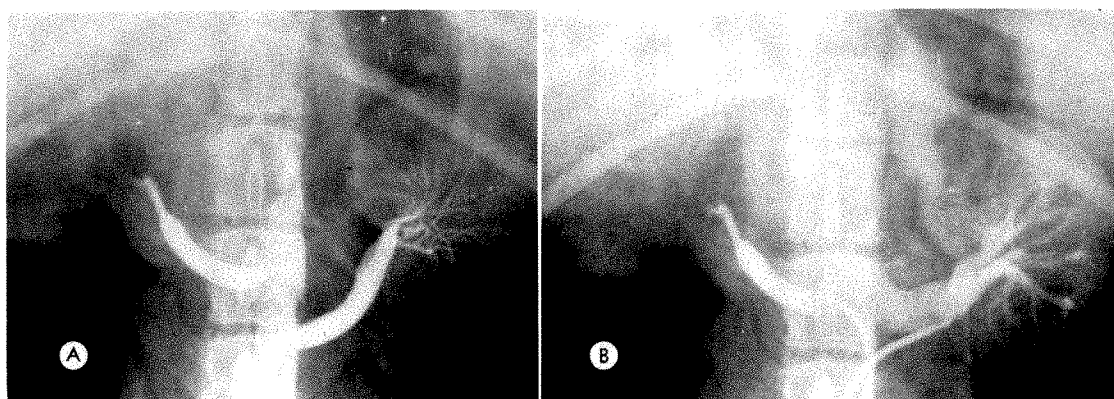


FIG. 7. (*A*) Simultaneous bilateral selective thorotrast angiogram immediately after injection of epinephrine, 30 μ g./kg., into the right renal artery (1 second film) shows "epinephrine changes" on the right. The angiogram of the left kidney is unchanged from its control appearance. (*B*) The 2.5 second study, 1.5 seconds after *A*, shows no progress of the opacified blood on the right. The left kidney shows normal venous opacification.

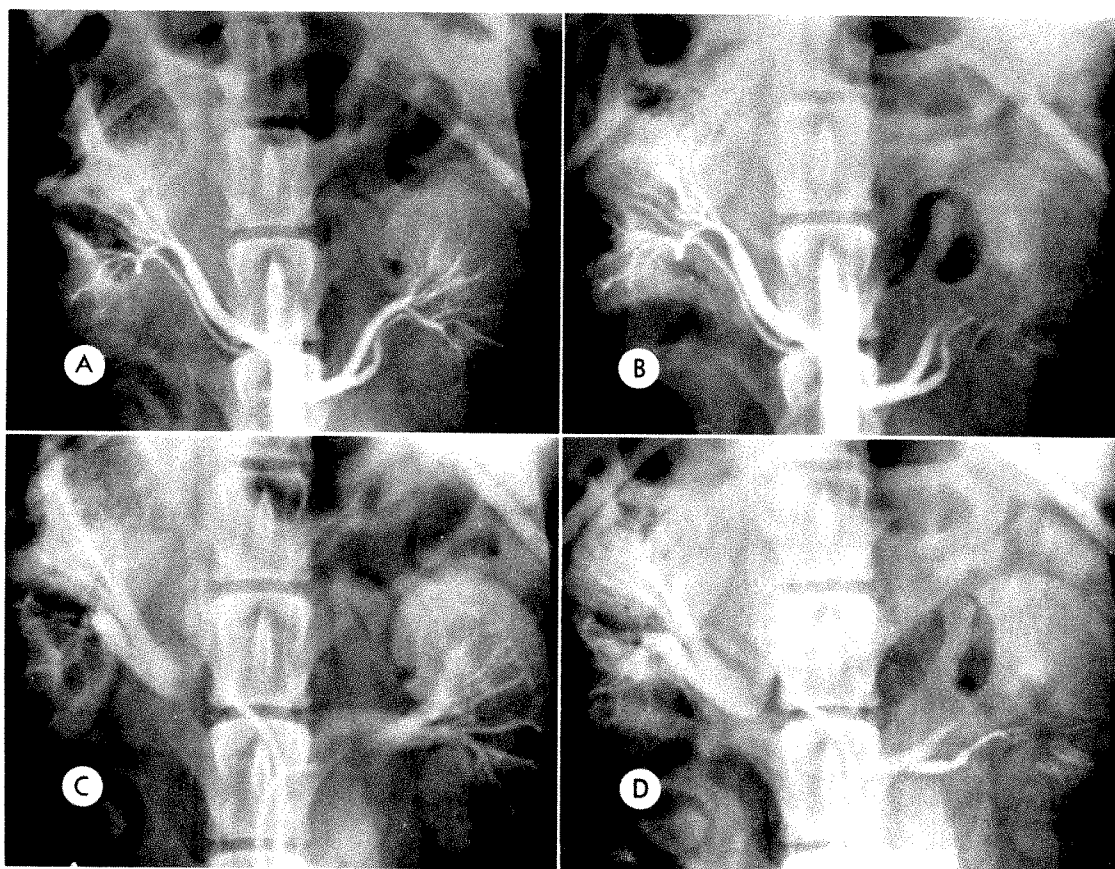


FIG. 8. (A) Control bilateral selective thorotrast angiogram (1 second film). (B) Bilateral selective thorotrast angiogram immediately after injection of levarterenol, $45 \mu\text{g.}/\text{kg.}$, into the left main renal artery (1 second film) shows marked constriction of the left arteries just beyond the bifurcation. The right renal angiogram remains normal. (C) Control bilateral selective angiogram (2.5 second film) shows good venous opacification bilaterally. (D) Post-direct-levarterenol bilateral angiogram, 1.5 seconds after B, shows no significant progress of the opacified bolus on the left. On the right the appearance is like that of the control (C) with good venous opacification.

A-D). Angiograms done 10 minutes later still showed marked differences in the two sides.

SHUNTS

Trueta *et al.*²¹ reported that intravenously administered adrenalin in dosage of 100 to $170 \mu\text{g. per kg.}$ in the rabbit caused a cessation of blood flow through the cortex; in some of their animals they demonstrated a juxtamedullary shunting of the blood. Montague and Wilson¹⁵ later also showed juxtamedullary shunts in the rabbit with epinephrine in intravenous dose of $100 \mu\text{g. per animal.}$ In none of our studies could the "Trueta shunt" be demonstrated in the

dog with either epinephrine or levarterenol, confirming the report of Moyer and Handley¹⁶ in this respect.

SUMMARY

Two vasopressors of the sympathicomimetic amine group—epinephrine and levarterenol—have been evaluated in respect to their effects on renal vascularity in the dog, as judged by angiography. Both drugs produced similar changes although levarterenol appeared more potent than epinephrine.

In small doses, these drugs showed changes suggesting increased vascular resistance at a level peripheral to the inter-

lobar arteries. In large doses they caused constriction of major renal arteries.

Both drugs have a direct action on the renal vasculature.

Juxtamedullary shunts could not be demonstrated.

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MORPHOLOGIC RESPONSES TO RENAL ARTERIAL PERFUSION WITH HYPAQUE*

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ADVERSE reactions to radiographic contrast media have been of concern since their introduction into clinical radiology. The exact incidence of serious complications following their use in diagnostic procedures is not known with certainty. Nesbit²⁵ reported that severe reactions of an allergic nature or shock occurred in approximately 1 in 500 injections for intravenous pyelography, although only 1 fatality occurred in 144,000 examinations. In reviewing 15 years experience with intravenous urography, Pendergrass *et al.*²⁶ noted a relatively constant mortality rate of about 8.6 per million injections in spite of an ever increasing number of examinations and the continuing introduction of new contrast agents. On the other hand, in a review of 13,207 abdominal aortographies, McAfee²¹ found an over-all incidence of fatal and serious nonfatal reactions of approximately 1 per cent. If these figures are extrapolated for comparison to those of Pendergrass *et al.*, the mortality rate would be about 2,800 per million examinations. This represents a 350 fold increase with the use of intra-arterial as compared to intravenous administration.

The basic cause of most reactions is unknown, but much investigation into possible etiologic mechanisms has been undertaken.

Read²⁷ and Dean *et al.*⁷ have studied the effects of radiographic contrast media in the pulmonary and renal circulations. Injection into the pulmonary artery was followed by an increase in pulmonary pressure, a decrease in systemic pressure and electrocardiographic abnormalities.

In dogs whose kidneys were perfused with a bypass system from the carotid artery, injection of contrast media produced a marked immediate increase in resistance to blood flow. These changes are dependent upon the presence of red blood cells and do not occur with saline or plasma perfusion. Evidence has been presented that the observed changes result from crenation and agglutination of erythrocytes produced by the hypertonicity of the contrast media.^{7,11,28}

Bernstein *et al.*³ investigated the effects of 90 per cent hypaque in dogs, simulating the technique of intravenous aortography. Fatal results were associated with pulmonary congestion, hemorrhage, and edema, as well as electrocardiographic changes of ischemia and rhythm disturbance. In a subsequent study, red blood cell aggregation was observed in the conjunctival capillaries after the intravenous administration of the same media.² These phenomena also have been observed by Gelin and his colleagues^{1,9,12,13} in patients with burns and other forms of trauma, and support the observations cited above.

Sobin *et al.*³¹ examined the capillary circulation of the conjunctiva in 24 patients following intravenous pyelography with 50 per cent hypaque and found erythrocyte agglutination and vasoconstriction in 20, but no actual stasis. The onset of these changes in the microcirculation occurred 2-3 minutes after injection, reached a maximum in 4-6 minutes, and was usually followed by total regression within 20 minutes.

Wiedman³⁴ examined the microcircula-

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tory changes in the bat wing after intra-arterial injection of radiographic contrast media. She observed vascular narrowing, crenation and agglutination of erythrocytes, and evidence of endothelial damage manifested by the adherence of leukocytes to the vascular lining.

Lasser *et al.*¹⁸ and Morris and his co-workers²³ studied changes in renal function after intra-arterial injections of various contrast media and found good correlation of toxicity with the duration of retention of contrast material in the kidney. Microscopic examination of the kidneys revealed engorgement, varying degrees of tubular necrosis, and cortical infarction. The changes were attributed to vascular spasm with prolonged retention of the contrast materials. Likewise, Helander¹⁵ noted renal tubular damage and frequent cortical infarction after intra-arterial injection of contrast media in 14 of 22 animals and concluded that if the angiogram was normal then it was unlikely to be associated with any serious morphologic change. If the angiogram was abnormal, however, as manifested by persistence of the arterial phase, abnormal prolongation of the nephrographic effect or with ragged, irregular accumulations of the contrast material, then invariably pronounced morphologic and functional change would be present.

Nesbit²⁵ has suggested that antigen-antibody reactions may be of importance and that premedication with antihistamines would be of value. However, Sandström²⁹ has convincingly challenged the role of immunology in the pathogenesis of reactions.

Lasser *et al.*¹⁹ studied the physical-chemical basis for toxic reactions and demonstrated a direct correlation of toxicity with the degree of protein binding to albumen by contrast media. Slight differences in chemical structure of the various contrast materials, particularly the presence or absence of a prosthetic group in the 5 position of the benzene ring, were suggested as being important determinants of binding affinity. The presence of a substituent in this position resulted in poor binding potential.

Davis,⁵ by modifying the plasma recalcification test to yield control values parallel to the Lee White clotting time of whole blood, has shown that all radiographic contrast media shorten the recalcified plasma clotting time by 50 to 70 per cent. In a fibrinogen-thrombin model, similar results were obtained, indicating that these media alter the colloidal stability of fibrinogen. Thus a pre-coagulant tendency is inferred.

It is probable that rheologic changes occur in practically every instance in which intravascular contrast media are employed.³¹ Yet the fact remains that in the majority of cases these changes produce no detectable, deleterious clinical effects. It is of more than passing interest that one-half of the fatal and one-fourth of the serious, nonfatal reactions noted by McAfee were of renal origin. While volume, speed, and anatomic site of injection as well as the clinical status of the patient are definitely of importance, no obvious explanation exists for the occurrence of reactions in some instances but not in others. As noted previously, adverse responses also occur much more frequently after intra-arterial injection. Recent reports suggest that low molecular weight dextran may be of benefit in reducing the frequency of untoward reactions to radiographic contrast media.^{2,30} The present investigation was designed to further study the effects of contrast media upon the renal circulation and to investigate possible methods of providing protection.

MATERIAL AND METHODS

Adult beagle dogs were anesthetized with nembutal and divided into two experimental groups.

GROUP I

Celiotomy was performed and the aorta and both renal arteries were identified. An umbilical tape was passed around the aorta between the origins of the right and left renal arteries so that when the tape was tightened, flow to the left kidney was occluded, but flow to the right was pre-

served. A second tape was passed around the aorta 3 to 4 cm. distal to the first to permit occlusion of the distal aorta. A No. 6 French N.I.H. catheter was passed retrograde through the femoral artery and positioned opposite the orifice of the left renal artery. Hypaque 50 per cent (diatrizoate sodium), 3 ml./kg., was injected by hand in less than 15 seconds into all but one dog who received 2.5 ml./kg. Immediately prior to injection, both tapes were tightened to occlude flow. Fifteen seconds after injection, the proximal tourniquet was released and 3 minutes after injection the distal tourniquet was released. The incisions were closed and the animals were returned to their cages. The group was further subdivided into animals who received no pre-treatment and those who received 1 per cent of their body weight as low molecular dextran (mw 40,000) or commercial American weight dextran (mw 75,000) intravascularly 15 minutes before injection.

GROUP II

The operative procedure in this group was modified in that the aorta proximal to the renal arteries was not occluded. A loop of suture was passed around the right renal artery to permit transient occlusion and an umbilical tape was passed around the distal aorta. A No. 6 French N.I.H. catheter was passed retrograde through the femoral artery and positioned opposite the orifice of the left renal artery. Hypaque 50 per cent, 3 ml./kg., was injected through the catheter by hand in less than 15 seconds. Immediately prior to the injection, the blood flow to the right kidney and to the distal aorta was occluded. Thirty seconds following injection, occlusion of the right renal artery was released and 3 minutes after injection the occlusion of the distal aorta was released. This group was also further subdivided into animals who received no pre-treatment and those who received 1 per cent of their body weight of either commercial American dextran or 0.9 per cent NaCl intravascularly, 15 minutes before injection. Cinefluorography was performed during injection in this group.

TABLE I
RESULTS OF INTRA-ARTERIAL INJECTION OF
HYPAQUE IN ANIMALS DURING COMPLETE
STASIS (GROUP I)

Dog No.	Dose ml./kg.	Pre-treatment	Right Kidney	Left Kidney
24	2.5	None	Excluded	Negative
25	3.0	None	Excluded	Infarcted
26	3.0	LM Dx	Excluded	Infarcted
27	3.0	LM Dx	Excluded	Infarcted
28	3.0	Am Dx	Excluded	Negative
30	3.0	Am Dx	Excluded	Infarcted

LM Dx=low molecular dextran (mw 40,000).

Am Dx=commercial American weight dextran (mw 75,000).

The animals were anesthetized 24 to 72 hours after surgery, both kidneys were removed and the animals were sacrificed. The kidneys were fixed in formalin and examined after hematoxylin and eosin staining.

RESULTS

In Tables I and II the results obtained in the two groups are summarized.

GROUP I—COMPLETE STASIS DURING INJECTION

(a) *Without pre-treatment.* These animals received neither saline nor dextran before injection. In 1 animal no gross or microscopic lesions were noted. This is the only animal in either group who received less

TABLE II
RESULTS IN INTRA-ARTERIAL INJECTION OF
HYPAQUE IN ANIMALS WITHOUT OBSTRUCTION
TO RENAL BLOOD FLOW
(GROUP II)

Dog No.	Dose ml./kg.	Pre-treatment	Right Kidney	Left Kidney
34	3.0	0.9% NaCl	Excluded	Negative
50	3.0	0.9% NaCl	Excluded	Negative
35	3.0	Am Dx	Excluded	Negative
49	3.0	Am Dx	Excluded	Negative
47	3.0	None	Excluded	Medullary Infarct
36	3.0	None	Excluded	Cortical Infarct
48	3.0	None	Excluded	Negative

Am Dx=commercial American weight dextran (mw 75,000).

than 3.0 ml./kg. of hypaque 50 per cent. In the second animal a pale, wedge shaped area was present in the cortex on cut section. Microscopically, thrombi were noted in the larger vessels. Areas of coagulation necrosis with pyknosis and karyorrhexis of the nuclei were observed while the periphery of the lesion was surrounded by interstitial hemorrhage and congestion. Figure 1 demonstrates a thrombus in an intrarenal artery while Figure 2 shows the histologic changes of renal infarction.

(b) *Pre-treatment with low molecular weight dextran.* One animal showed histologic evidence of thrombi and infarction in the left kidney. The kidney of the other dog was histologically normal.

(c) *Pre-treatment with commercial American weight dextran.* Histologic evidence of thrombosis and infarction was noted in the left kidney of both animals.

Examination of the right kidney of all animals was normal.

GROUP II—CONTINUED ARTERIAL PERFUSION DURING INJECTION

(a) *Without pre-treatment.* One dog showed no gross or microscopic evidence of abnormality. Of the others, 1 showed medullary infarction and 1 cortical infarction in the left kidney. In these, cinefluorography revealed straightening of the renal arteries, multiple parenchymal filling de-

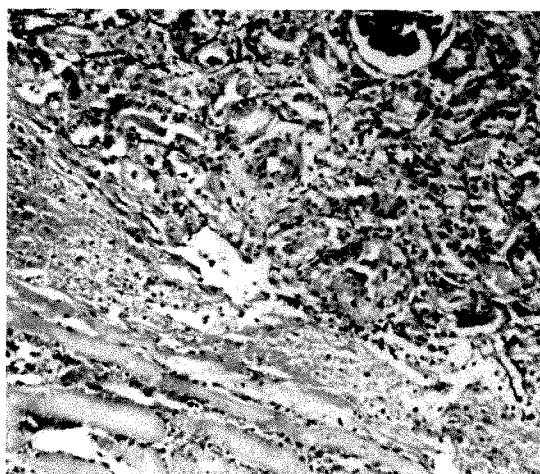


FIG. 2. Typical histologic pattern of renal infarction after hypaque perfusion.

fects and a prolonged nephrographic phase. These findings correlated with areas of gross and microscopic infarction noted on pathologic examination of the kidneys.

(b) *Pre-treatment with American weight dextran.* No abnormality was noted in the left kidney of either animal.

(c) *Pre-treatment with 0.9 per cent NaCl.* No abnormality was noted in the left kidney of either animal.

Examination of the right kidney in all animals was normal.

Comments. Of the animals in which complete stasis was obtained prior to injection of hypaque 50 per cent and which received 3 ml./kg., 80 per cent developed histologic evidence of thrombosis and infarction. The single animal receiving less than this volume showed no gross or histologic changes. The single animal receiving this volume of contrast material which failed to show any histologic lesion was pre-treated with low molecular weight dextran. Of the animals in which continued perfusion of the kidney was permitted, only 2 (28 per cent) showed morphologic damage. Cinefluorographic study in these animals revealed the changes described by Helander as being associated with morphologic damage.¹⁵ Because of the time interval involved between injection and sacrifice of the animals, transient morphologic change as noted by others¹⁶ may have been missed.

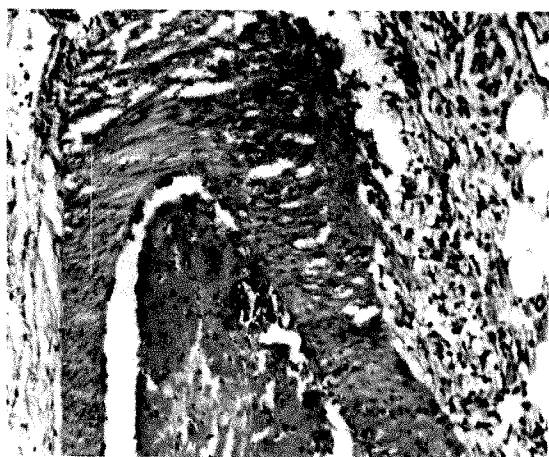


FIG. 1. Thrombus in larger renal vessel after hypaque administration.

DISCUSSION

In a study of the effects of contrast material on the kidney of rabbits, Idbohrn and Berg,¹⁶ using a technique similar to that employed in our Group I experiments, were able to produce morphologic changes of proteinaceous exudation, tubular epithelial necrosis, and cortical infarction. With the exception of infarction, most of the changes were reversible and regeneration was rapid. Contrary to our findings, however, no thrombi were found in the histologic sections despite careful search. In their study, increasing the concentration of the contrast material above a certain critical level was not accompanied by an increase in the severity of the injury produced. However, direct injection of the contrast media into a renal artery was followed by more severe injury. In a subsequent publication reviewing clinical reactions to renography, Idbohrn¹⁷ did note a correlation between concentration and toxicity and again warned of the hazards of direct renal arterial injection. In this regard, Mullady *et al.*²⁴ produced renal functional impairment with injection of hypaque directly into the renal artery of dogs. Significant decreases in PAH and creatinine clearances were documented.

At the present time, it is felt that two of the major, if not the most important, mechanisms involved in the production of adverse effects by radiographic contrast media are the development of vasoconstriction, and red blood cell crenation and agglutination. The former may be the result of damage of the endothelial lining by direct contact with the media,^{25,27} or may be mediated by protein binding in the vascular wall.¹⁹ The latter might result solely from the exposure of circulating erythrocytes to a very hypertonic environment¹¹ or stem from interference with the physiologic dispersing effects of albumen through protein binding with the medium.¹⁹

In a recent review, Wells²⁸ has pointed out that fibrinogen plays a major role in the production of red blood cell aggregation in the microcirculation by altering the balance

of dispersing and aggregating forces. Although not as yet evaluated, an alternate hypothesis would suggest that changes in fibrinogen might be of importance in these reactions. Fibrinogen changes are known to occur in burns, trauma, and other conditions of stress and parallel changes in the suspension stability of the blood.^{8,26} The production of microscopic sludging in the conjunctival capillaries³¹ with hypaque 50 per cent, a substance with little protein binding effect, would suggest that study of the role of fibrinogen might be a fertile field of investigation.

The importance of changes in the coagulation system requires further investigation before definite conclusions can be drawn. Davis⁵ has shown that shortening of the plasma recalcification time is consistently reproducible *in vitro* with all commercially available contrast media. In preliminary work with both animals and humans undergoing urographic examinations, he has found consistent *in vivo* shortening of the whole blood clotting time after intravenous administration of many agents.⁹ However, the decrease in clotting time does not seem to have any readily apparent clinical significance in the usual case presenting for radiographic examination. On the other hand, in instances where erythrocyte aggregation and stasis are present, the formation of fibrin might convert a transient phenomenon into a permanent thrombus. Thus, the previously described evanescent changes would become irreversible. In analysis of the present study, the single consistent factor which resulted in almost invariable histologic damage was stasis plus the introduction of contrast media, producing thrombosis and infarction. In the control kidney in Group II, stasis alone did not result in any morphologic change. Likewise an equal volume of contrast material in Group II without stasis did not produce consistent change. Apparently, dilution during unimpeded flow offered some protective action. In vascular disease with significant degrees of vessel narrowing and obstruction, flow may

well be reduced and the possibilities of injury are therefore increased. The volume of contrast media used in this investigation is considerably greater than that used clinically. In disease states, however, regional flow is frequently altered and media may enter various channels in larger amounts than anticipated, as noted in some of the cases reviewed by McAfee and Wilson.²⁰

Study of the pathogenesis of reactions to contrast media has stimulated interest in the investigation of methods to prevent them or to reduce the frequency of their occurrence. Because changes in the microcirculation seem to be of great importance, agents altering microcirculatory events have received wide attention.

Much has been written about the use of low molecular weight dextran (mw 40,000) in protecting against intravascular red blood cell agglutination. Gelin and his associates^{1,9} have shown its beneficial effects in various surgical and experimental conditions. Finsterbusch *et al.*¹⁰ demonstrated a protective effect on the renal circulation when low molecular weight dextran was used in extracorporeal circulation. In dogs, Bernstein and Evans² reported an increase in the LD₅₀ of hypaque 90 per cent given intravenously from 3 ml./kg. to 6.5 ml./kg. and an increase in the maximal nonlethal dose from 2 ml./kg. to 4 ml./kg. Sessions, Killen and Foster³⁰ demonstrated that low molecular dextran reduced the renal and central nervous system toxic effects from the injection of urokon. Bernstein *et al.*⁴ showed that low molecular weight dextran caused a significant rise in red blood cell negativity and thus theoretically in mutual repulsion. Thorsen and Hint³² indicate that low molecular weight dextran also seems to influence the protein envelope of aggregated blood cells. Gelin, Sölvell and Zederfeldt¹⁴ have shown that both low molecular weight and commercial American weight (mw 75,000) are plasma volume expanders. On the other hand, Garber and Read¹¹ were unable to show any protective effect of low molecular weight dextran upon the pulmonary circulation following injection of

contrast media that was distinct from any other volume expander. Wiedman³⁵ has offered supporting evidence from direct microscopic observation of changes in the microcirculation. Neither prior injection of low molecular weight dextran nor its subsequent infusion reversed red blood cell aggregation or prevented vascular narrowing. Increased flow seemed related only to increased volume.

The present study has failed to demonstrate any significant protective effect against morphologic damage to the kidney with either 40,000 or 75,000 molecular weight dextran when stasis was present.

In the absence of stasis, 2 of 3 unprotected animals developed renal infarction. The other dogs who received pre-treatment with saline or commercial American weight dextran had undamaged kidneys on gross and microscopic examination. In this group of animals, pre-treatment seemed to offer protection against morphologic damage.

The present study indicates that for a given volume and concentration of radiographic contrast media, histologic change is correlated with stasis and conversely the absence of stasis is associated with the irregular occurrence of morphologic change. We suggest, however, that premedication with a volume expander be seriously considered in all patients undergoing arteriographic examinations. Because of the work of investigators cited previously, low molecular dextran might be the agent of choice.

SUMMARY

Morphologic changes in dog kidneys following the intra-aortic injection of hypaque are presented. The significance of various pathogenetic mechanisms and possible protective measures are discussed.

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OSTEOSCLEROSIS OCCURRING IN RENAL DISEASE*

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OSTEOMALACIA and secondary hyperparathyroidism are the common and expected complications of chronic renal diseases.⁴ Osteosclerotic changes are less common but have been reported recently as occurring in 20 per cent of patients who had skeletal changes resulting from chronic uremia.¹⁰ Osteosclerosis is infrequently encountered in hyperparathyroidism, although the possible association of the sclerosis with the function of the parathyroid gland is often suggested in the literature.^{5,9,11}

Our discussion of the osteosclerosis seen in renal disease centers about a case wherein this complication appeared following the institution of corrective measures for acidosis and calcium loss and, in turn, disappeared when the supplemental dietary calcium and vitamin D therapy was discontinued.

REPORT OF A CASE

This 35 year old Caucasian woman was first seen in January, 1960 with an established diagnosis of bilateral chronic pyelonephritis. Physical examination was negative and urinalysis revealed an alkaline urine containing cellular elements, a trace of albumin, many bacilli and a specific gravity of 1.010. Faint visualization with changes of chronic pyelonephritis was present in both kidneys on excretory urography, and calculi were noted in the right kidney. The serum electrolytes at this time were sodium 146 mEq./L., potassium 3.6 mEq./L., chlorides 123 mEq./L., bicarbonate 10 mEq./L., calcium 8 mg. per cent and phosphorus 2.6 mg. per cent; alkaline phosphatase was 26 King Armstrong units. The 24 hour calcium excretion was 350 mg. on a low calcium diet. Renal function tests disclosed a blood urea nitrogen of 15 mg. per cent, serum creatinine of 1.5 mg. per cent and a creatinine clearance of 90 liters in 24 hours; the 15 minute phenolsulfonphthalein test was 6 per cent.

On the basis of these studies, the following

conclusions were reached: The chronic pyelonephritis led to impaired tubular function which resulted in renal tubular acidosis. The chronic acidosis caused an increased mobilization of calcium from the skeleton with resultant hypercalciuria and renal calculi. This interpretation was supported by a demonstrated osteomalacia in the roentgenograms and complaints of joint stiffness in the patient (Fig. 1).

The therapy that was instituted to correct the calcium imbalance and the acidosis consisted of Shohl's solution, Randall's solution, calcium gluconate and vitamin D. Four months after starting the regimen, her joint stiffness disappeared. A right pyelolithotomy was carried out 9 months later when the patient re-entered the hospital with right urinary tract obstruction.

Eighteen months after her first visit, osteosclerosis involving the lumbar spine, pelvis and proximal femora was observed on the pyelogram (Fig. 2). A skeletal survey was not conducted. Accordingly, the supplemental vitamin D and calcium therapy was stopped, but the Shohl's and Randall's solutions were continued. The electrolytes at this time were sodium 140 mEq./L., potassium 5.2 mEq./L., chlorides 104 mEq./L., bicarbonate 18 mEq./L., calcium 9 mg. per cent and phosphorus 4.1 mg. per cent. Serum creatinine was 1.54 mg. per cent.

She continues to be observed and when last seen was alive and active. One and one-half years after the calcium and vitamin D were discontinued, her skeleton appeared normal (Fig. 3). Her final laboratory studies included a urine specific gravity of 1.010, hemoglobin 12 gm., serum creatinine 1.2 mg. per cent, blood urea nitrogen 17 mg. per cent, serum calcium 9.6 mg. per cent, serum phosphorus 3.6 mg. per cent, alkaline phosphatase 6.5 King Armstrong units and a 15 minute phenolsulfonphthalein excretion test of 5 per cent.

DISCUSSION

Rutishauser⁶ and his supporters⁴ have emphasized the importance of renal tubular acidosis in the production of osteosclerosis. The fluctuations of the renal insufficiency

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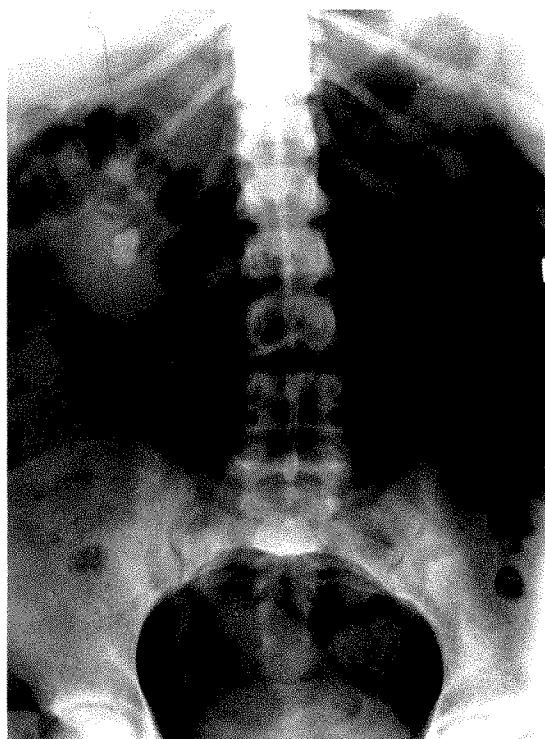


FIG. 1. One hour excretory urogram demonstrating right renal calculi and osteomalacia.

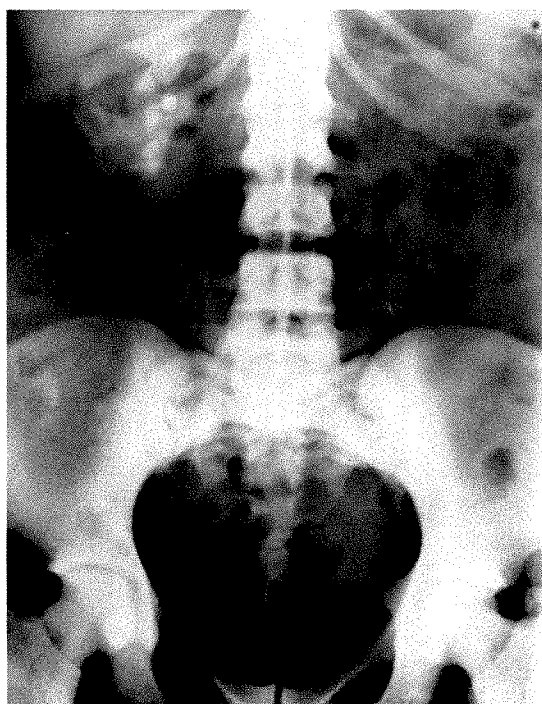


FIG. 2. Ten minute excretory urogram demonstrating osteosclerosis after 18 months of therapy.

are believed to produce periods of new bone formation which can predominate and produce osteosclerosis.

The characteristic occurrence of osteosclerosis in the lumbar spine, pelvis and skull led Crawford *et al.*² to believe that the chronic anemia of renal failure was responsible as these bones were those of most active hematopoiesis.

Jaffe⁵ described the subchondral condensation of spongiosa in the vertebrae at the vertebral end plates in patients affected with osteitis fibrosa due to primary hyperparathyroidism. Beveridge and his associates¹ discussed the fact that this curious layering of vertebral sclerosis is found only in the osteosclerosis of renal failure or hyperparathyroidism. They published a case of primary hyperparathyroidism associated with renal failure and osteosclerosis.

Cronqvist³ noted the regression of rachitic changes after protracted treatment of renal tubular acidosis in a 17 year old patient with an 8 year history of chronic renal disease.

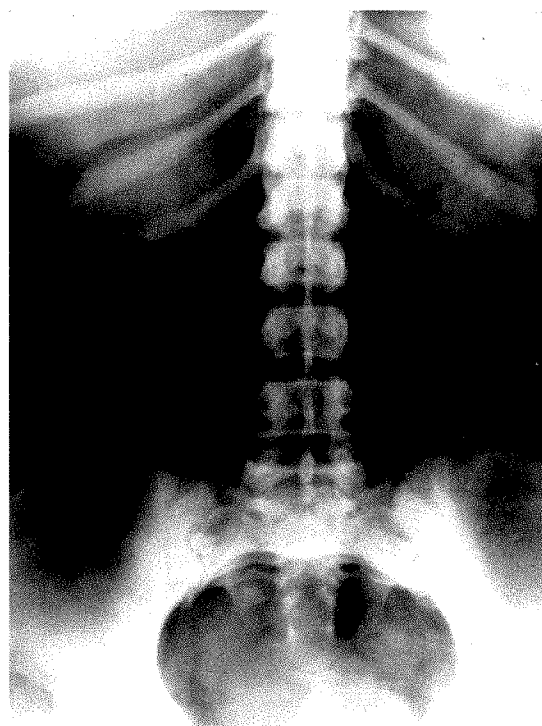


FIG. 3. Supine roentgenogram of abdomen 18 months after cessation of recalcification therapy demonstrating normal skeletal density.

Shapiro⁷ studied a patient with typical osteitis fibrosa whose skeleton became densely sclerotic after extirpation of a parathyroid adenoma. He attributed this metamorphosis to an exaggerated healing response.

Stanbury⁸ has warned against the usage of vitamin D therapy in individuals with osteitis fibrosa and has advised against aiming at a restoration of normal skeletal appearance on the roentgenogram; he stated that symptomatic relief was a reasonable goal. In his published illustrations osteosclerosis and soft tissue metastatic calcification in these patients were demonstrated. He considers patients with osteomalacia less prone to complications requiring recalcification regimen. Stanbury also believes that osteomalacia of osteitis fibrosa may result from an acquired insensitivity to the action of vitamin D which inhibits absorption of calcium from the gut.

Our patient is the first to be reported who demonstrated regression of the osteosclerosis when the supplemental calcium and vitamin D were stopped. It is our interpretation that the renal tubular acidosis is the inciting cause, producing through the calcium loss the commonly observed osteomalacia.

The osteomalacia in turn stimulates increased osteoblastic activity as evidenced by the rise in alkaline phosphatase. When the acidosis is corrected and calcium is made available to the skeleton, recalcification occurs at an accelerated rate. If the physician continues to give large amounts of calcium along with vitamin D, the osteoblasts will persist in depositing calcium beyond that required for normal bone density and osteosclerosis will occur. It is postulated that perhaps the long-standing osteomalacia has stimulated the osteocytes to produce an abnormal amount of osteoblasts or abnormal hyperfunction of the osteoblasts so that their activity was not normally inhibited by adequate repletion of the bone with minerals. The experience gained in this case would suggest that the physician must follow a patient on a recalcification regimen closely in order to detect the first indication of osteosclerosis.

When it appears, it can be arrested or reversed by deleting the excess oral calcium and vitamin D therapy. If one desires to recalcify the bone at a slower rate and avoid osteosclerosis, it is necessary to treat only the systemic acidosis with Shohl's and Randall's solutions.

SUMMARY

A discussion of the causes of osteosclerosis resulting from chronic renal disease is presented with a case report. The patient described demonstrated osteomalacia which changed to osteosclerosis when the renal tubular acidosis was corrected and a recalcification regimen was instituted. Cessation of the recalcification therapy resulted in a return to normal of the skeletal density.

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HEMATOLOGIC RESPONSES TO HUMAN WHOLE BODY IRRADIATION*

ANALYTIC APPROACHES TO BIOLOGIC DOSIMETRY

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THE depletion of formed circulating blood elements following exposure to ionizing radiation has been appreciated since the turn of the century.⁹ The significance of this phenomenon for human irradiation was emphasized by Minot and Spurling¹³ in 1924 who exposed 22 cancer patients to fractionated whole body doses of roentgen rays. They observed a gradual diminution of granulocytes during the first week, while an analysis of their reported counts shows an abrupt decline in lymphocytes during the first 24 hours, followed by a more gradual depression. The development of atomic weapons and nuclear power created the impetus for further detailed study of the hematologic effects of radiation in humans.^{1,2,7,8,10,18} The employment of whole body irradiation in the past several years for cancer therapy and in preparation for homotransplantation has provided considerable information with regard to the response in man, particularly in relation to carefully calculated doses.^{3,5,11,12,17}

In this study, hematologic data from 7 patients exposed to whole body radiation in preparation for renal homotransplantation have been analyzed from three points of view: (1) as an internal comparison among those patients receiving the *same* calculated dose, and between these patients as a group and individual patients receiving different dose schedules; (2) as an external comparison with the results reported from other centers; and (3) as an attempt to relate the degree of response observed to animal and human studies regarding bone marrow sensitivity.

METHOD

Patients were exposed to roentgen rays generated by a 250 kv. constant potential unit with Thoreus 3 filtration having a half value layer in Cu of 3 mm. Patients were coiled in a 120 cm. treatment oval with target to skin distances of 150 to 160 cm. to the flank.⁴ Doses are recorded as nominal in air, uncorrected for backscatter at the mid-sagittal plane of the flank, where the average dose rate was 5 to 5.5 r/min. Half the dose was administered with the patient lying on one side, half with him lying on the other. The maximum to minimum inhomogeneity of the absorbed dose in the mid-sagittal plane was determined to be of the order of 30 per cent.

The analysis of the hematologic data was retrospective. Routine white blood cell counts and smears were made by the hospital blood laboratory using standard methods and counting chambers. Direct phase counting of platelets was employed, and reticulocyte levels were assayed by cresyl blue staining.

THE INDEX GROUP

Three patients received an identical dose schedule: 250 r separated by 7 days from a second exposure of 200 r. These patients, singly and together, represent an index group with which the remaining patients and those of other centers have been compared.

Figure 1 graphically shows the raw data from a single patient (J.R.) who successfully accepted a renal homograft from a non-identical twin brother. He received a

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From the Harvard Medical School Department of Radiology at the Peter Bent Brigham Hospital.

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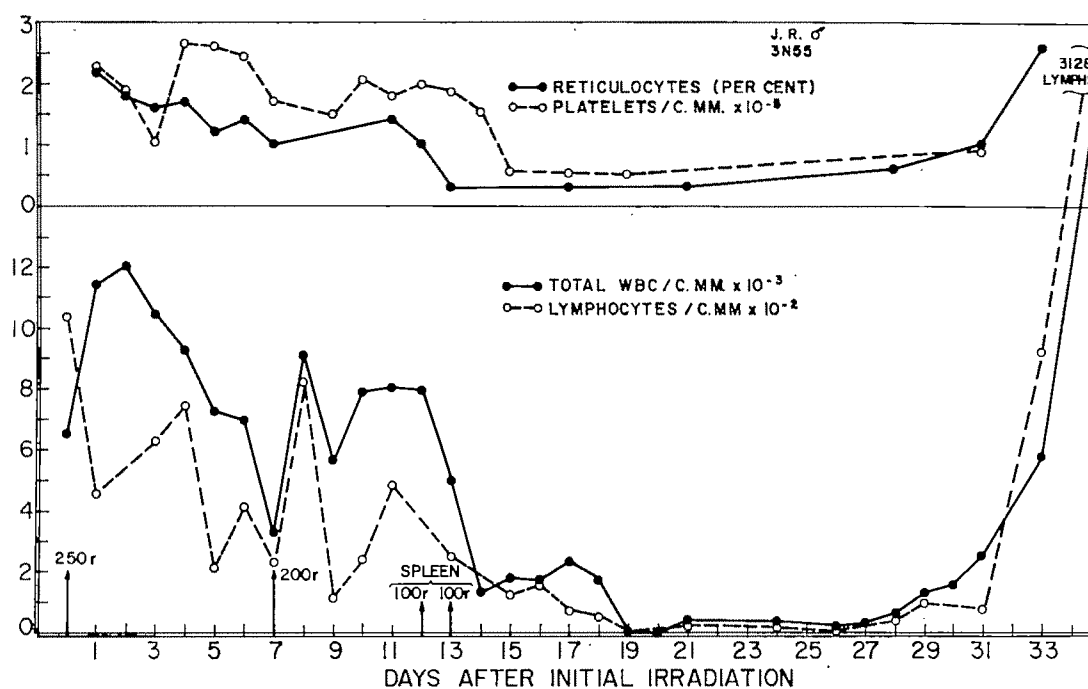


FIG. 1. Hematologic responses of patient J.R.

total of 450 r in 2 doses, as well as supplemental splenic irradiation. White and lymph cell counts reached a minimum in the third week and began to recover by the fifth, with a marked overshoot. By the end of the second week platelets and reticulocytes had declined maximally.

In Figure 2 the hematologic data from a second patient (R.D.) are presented. No initial lymphocyte count was recorded for this patient. Leukocytes and lymphocytes reached minimal levels on days 16 and 17 respectively, reticulocytes on day 9 and platelets on day 17.

Figure 3 shows similar data for another patient (R.R.) exposed to the same dosage schedule. For this patient, as well as the first (J.R.), the lymphocytes showed a prompt decline of about 50 per cent in the first 24 hours with a more gradual fall thereafter. The white and reticulocyte cell counts reached a minimum on day 14, the platelets on day 18. In Figure 4 the same data for leukocytes and platelets are plotted on semilogarithmic coordinates. The fit to an exponential survival function is reason-

ably close during the first 11 to 13 days with an estimated 50 per cent reduction time of 6 days for white cells and of 8 days for platelets.

Composite leukocyte counts for the

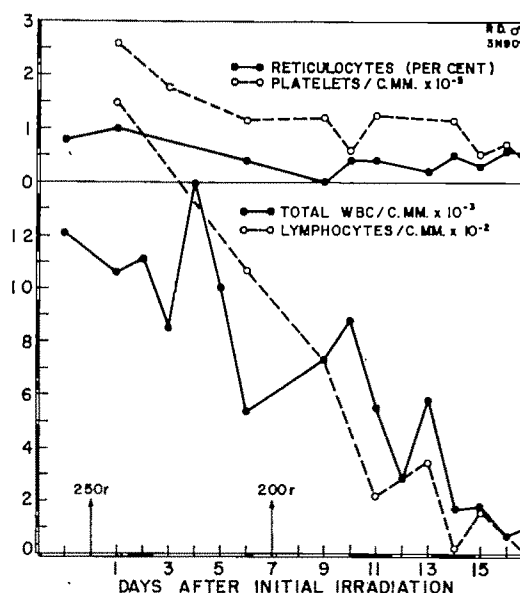


FIG. 2. Hematologic responses of patient R.D.

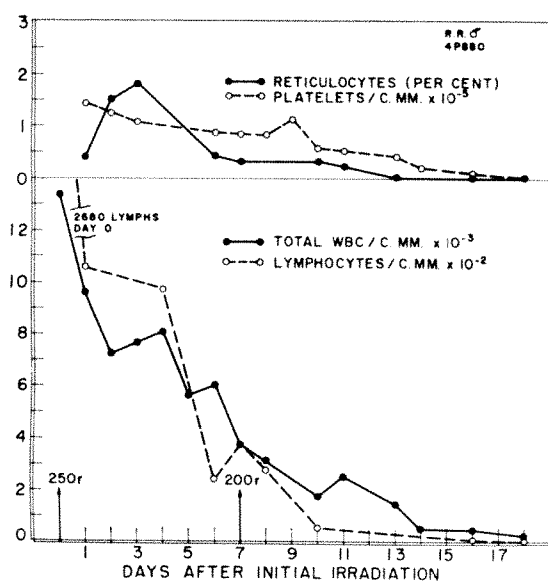


Fig. 3. Hematologic responses of patient R.R.

index cases are shown in Figure 5. Although there is considerable variability in the day-to-day response of each patient, there are points of intersection at about day 6 and again at days 14 to 16. The general trends are more clearly defined in Figure 6 which shows the *mean* leukocyte and lymphocyte counts for the same patients. The total white cell count has fallen about 40 per cent in the first week and is followed by a plateau. Following a secondary decline, the over-all decrease after the second week is 87 per cent. The lymphocytes show an

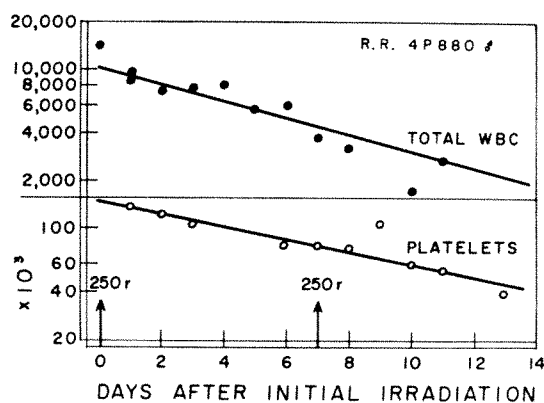


Fig. 4. Total leukocyte and platelet responses of patient R.R. plotted on semilogarithmic coordinates

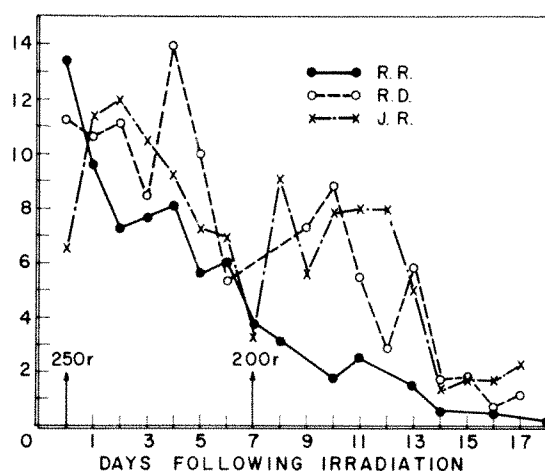
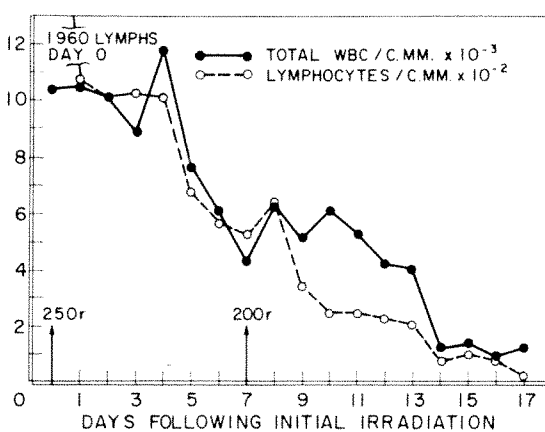


Fig. 5. Composite total leukocyte responses of patients R.R., R.D. and J.R., comprising the "index group."

initial fall of approximately 50 per cent in the first day with another 50 per cent fall on days 1 to 7. The over-all decline by day 14 to 16 is about 95 per cent. The initial, prompt diminution of lymphocytes has been observed repeatedly and is due presumably to a direct effect on circulating cells.

In Figure 7 the granulocyte and lymphocyte counts for the first 2 weeks are presented on semilogarithmic coordinates. Least square lines have been fitted and

Fig. 6. Mean total leukocyte and lymphocyte responses of the "index group," linear coordinates. (Reprinted from the *Ann. of N. Y. Acad. of Sci.*, 1964, 114, 168, with the permission of the New York Academy of Sciences.)

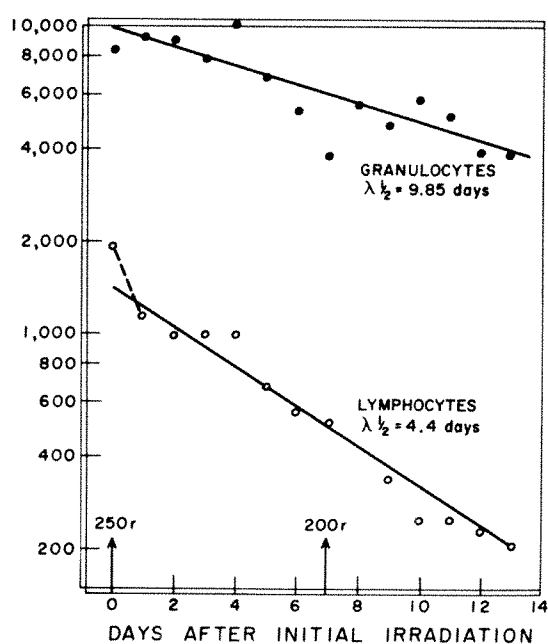


FIG. 7. Mean granulocyte and lymphocyte responses of the "index group," semilogarithmic coordinates.

drawn (these were calculated with the aid of a 1620 IBM computer generously made available by Dr. Anthony Bartholomay, Director of the Biomathematics Laboratory, Peter Bent Brigham Hospital). The computed half reduction time for granulocytes is 9.85 days, while the secondary decline in lymphocytes has a 50 per cent reduction in 4.4 days. The data fit exponential survival curves for the first 13 days only, the points falling off rapidly after that, possibly due to the influence of the second exposure.

In Figure 8 the mean platelet and reticulocyte cell counts are shown for the same 3 patients. Again, there is the suggestion of a plateau at the end of both the first and second weeks. The over-all decline in platelets is about 80 per cent and of reticulocytes 87 per cent. In Figure 9 the same data for weeks 1 and 2 are plotted on semilogarithmic coordinates. The reticulocyte points scatter considerably about the calculated least square line. The accuracy and precision in their determination are less than that for other elements, as they are scored

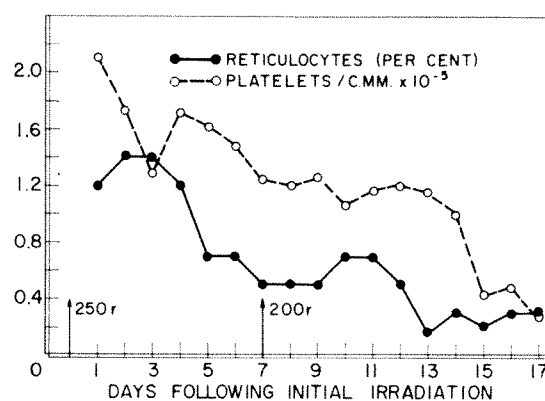


FIG. 8. Mean reticulocyte and platelet responses of the "index group," linear coordinates. (Reprinted from the *Ann. of N. Y. Acad. of Sci.*, 1964, 114: 168, with the permission of the New York Academy of Sciences.)

in tenths of a per cent of a variable red cell population. The computed half reduction time is 6 days. For the platelets the half reduction time is 15.9 days.

From the exponential curves, the relative disappearance rates of the 4 formed elements can be compared. In ascending order they are: lymphocytes 4 days, reticulocytes 6 days, granulocytes 10 days and platelets 16 days. This is consistent with the prompt disappearance of lymphocytes and reticulocytes and the delayed disappearance of platelets reported by others.^{8,11,17}

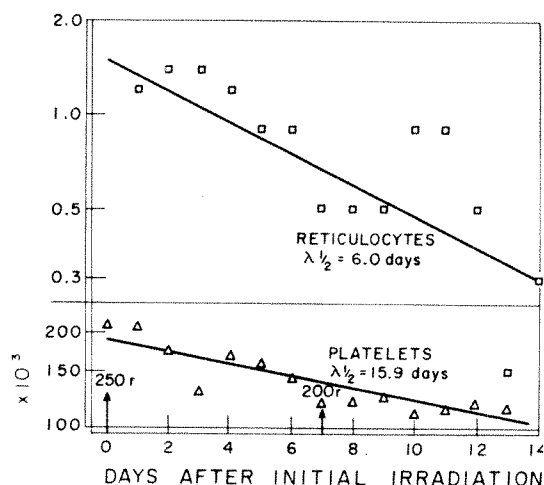


FIG. 9. Mean reticulocyte and platelet responses of the "index group," semilogarithmic coordinates.

TABLE I
GRANULOCYTE AND LYMPHOCYTE RESPONSES

Patient (dose)	Granulocytes			Lymphocytes		
	Maximum Depression		Half Reduction	Maximum Depression		Half Reduction
	Day	Per Cent	Days	Day	Per Cent	Days
1. 3 Patients—index group (250 r-7 da.-200 r)	16	89	9.9	17	98	4.4
2. M.C. 7N278 (250 r-7 da.-150 r)	19	97	7.5	19	99	6.8
3. A.Q. 4P545 (120 r-3 da.-120 r-4 da.- 100 r)	14	61	9.8	11	92	6.5
4. C.W. 9G318 (150 r-2 da.-100 r)	8	75	—	7	92	—

REMAINING CASES

Table I is a summary of the granulocyte and lymphocyte responses for 3 patients as compared with the index group presented on the top line. The cases are ranked in order of decreasing total dose. The time of maximum depression, the degree of maximum depression and the initial half reduction time are given. A similar summary of platelet and reticulocyte responses is presented in Table II. An absent entry for the half reduction time indicates that insufficient data were collected during the first week to compute this figure accurately.

In general, the maximum depression of the formed elements has some dose dependence in this range, but there is considerable variation, particularly shown by Case 2 (M.C.), whose granulocyte and reticulocyte response was greater than that of the index group. If the per cent maximum depression for each element is given equal weight, the 3 patients can be scored relative to the index group adjusted to 100. The calculated scores are: (1) index group 100, (2) M.C. 104, (3) A.Q. 97, (4) C.W. 90. The average maximum per cent depressions of the 4 formed elements are: (1) index group

TABLE II
PLATELET AND RETICULOCYTE RESPONSES

Patient (dose)	Platelets			Reticulocytes		
	Maximum Depression		Half Reduction	Maximum Depression		Half Reduction
	Day	Per Cent	Days	Day	Per Cent	Days
1. 3 Patients—index group (250 r-7 da.-200 r)	17	87	15.9	13	87	6.0
2. M.C. 7N278 (250 r-7 da.-150 r)	19	80	—	9	100	—
3. A.Q. 4P545 120 r-3 da.-120 r-4 da.- 100 r)	18	92	18.2	15	86	7.4
4. C.W. 9G318 (150 r-2 da.-100 r)	9	75	—	10	83	—

90 per cent, (2) M.C. 94 per cent, (3) A.Q. 83 per cent, (4) G.W. 81 per cent—a difference of about 10 per cent over the dose range 250 to 450 r.

The half reduction times also show considerable variability, as they did among the 3 patients constituting the index group. The values given are for the *initial* disappearance rates computed from the hematologic data of the first 10 to 12 days. In general, for the individual patients, as for the index group, the points fall off rapidly from the exponential line after that time. This suggests that the initial disappearance rate is a reflection of the first radiation insult. The half reduction time for Patient 2 (M.C.) should, therefore, fall within the range of the index group since all patients received the same first dose. In fact, the initial disappearance rates of granulocytes and lymphocytes are greater for this patient than the mean value for the index group, but are well within the estimated range. Patient 3 (A.Q.) received a lower first dose than did the index group, followed 3 days later by an identical, second dose. The disappearance rates have been calculated in this instance for all 4 formed elements and, with the exception of granulocytes, are less than the index group values. The mean increase in half-reduction time for this patient, as compared with the index group, was 121 per cent, with a range of 99 per cent (granulocytes) to 149 per cent (lymphocytes) for the 4 blood elements.

COMPARISON WITH OTHER RESULTS

In order to integrate the hematologic responses of these patients with general medical experience, the granulocyte data of the index group were compared with another study¹² in which the radiation conditions were similar and sufficient hematologic details are provided. When data from this latter investigation are plotted on semilogarithmic coordinates, there is a linear decrease in the granulocytes beginning the day following irradiation and persisting into the second week. For patients receiving an average of 150 r, the half re-

duction time was 18.8 days, as compared with 9.85 days found for the index group of this study, which received an initial dose of 250 r (Fig. 10). This implies that about 100 r is required to double the radiation induced granulocyte disappearance rate. Although the absolute significance of this value cannot be determined from the type of measurements employed, it is of interest that the mitotic index of human bone marrow shows a 50 per cent depression at about 100 rads on the fourth day following exposure.⁶ In addition, the reproductive integrity of mouse bone marrow cells has been estimated to have a 37 per cent survival of 115 rads,¹⁶ and cultured mammalian cells are reported to have a mean lethal dose *in vitro* in the range of 100 rads under aerobic conditions¹⁵—all of the same order of magnitude.

For historic interest, the data of Minot and Spurling's study¹³ of 1924 are replotted on semilogarithmic coordinates in Figure 10. In addition, granulocyte data from a single patient exposed to a cobalt 60 source⁵ are also included. The conformity of the disappearance curves to an exponential function under these divergent exposure conditions suggests that initial disappear-

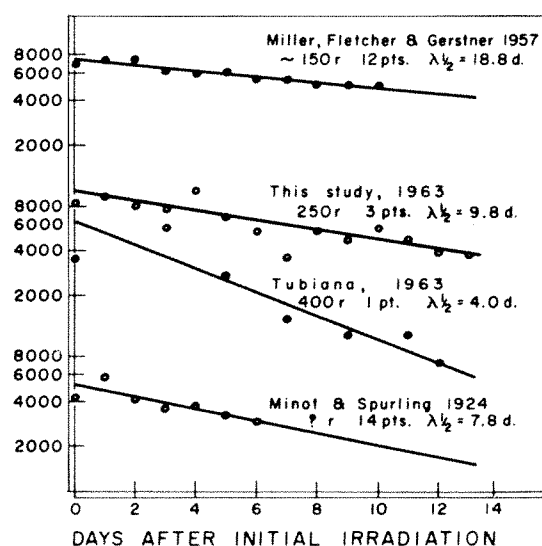


Fig. 10. Granulocyte responses of patients from other centers compared with the "index group," semilogarithmic coordinates (see text).

ance rates can be generally applied to the evaluation of hematologic responses following whole body irradiation. The construction of an appropriate dose-response curve from such disappearance rates might provide useful information in two areas. First, it would permit an early estimate of the equivalent biologic dose received by individuals accidentally exposed to radiation of the same quality. Second, a series of such curves could be employed to compare the relative biologic effectiveness of exposure to radiations of differing quality. Of course, such curves would be useful only in the moderate dose range, below that resulting in near complete inactivation of the sensitive marrow elements. At higher doses the disappearance rates would become asymptotic with the natural granulocyte survival.

The initial exponential decrease in granulocytes beginning on the first day following irradiation was not anticipated, since large doses of radiation in the dog and monkey lead to an exponential decline in granulocytes only after a latent period of 3 days.¹⁴ The prompt response in man suggests that the release of cells from the marrow, as well as marrow cell division, is affected by the radiation.

However, the response in patients receiving fractionated doses is somewhat paradoxical. Following the first dose, there is a prompt decline in the peripheral counts, but, following the second dose 1 week later, there is no deviation from the initial disappearance rate for nearly another 7 days. The reasons for the prompt response in the first instance and the delayed response in the second are unclear and will require further elaboration by comparing single and fractionated dose exposures. In some of the transplantation patients studied in this report, a deteriorating renal function during the third week may have influenced the hematologic responses occurring in that interval.

CONCLUSIONS

Hematologic data have been presented for 6 patients who received total body ir-

radiation in preparation for kidney transplantation.

Three patients (titled the "index group") received an identical dose schedule of 250 r, a 7 day interval, and then 200 r. Their average responses have been compared with those observed in other patients exposed to lower doses; the degree of maximal response exhibited some correlation with total dose over the relatively narrow range of 250 to 450 r.

For the index group, the exponential disappearance of lymphocytes, reticulocytes, granulocytes and platelets progressed in that order, with half reduction times in days of 4, 6, 10 and 16, respectively.

The exponential disappearance rate of granulocytes in the index group has been compared with another study¹² and certain similar features have been discussed in terms of marrow inhibition.

The early estimate of radiation damage permitted by the use of disappearance rates is an attractive feature and could be employed as an aid in planning optimum treatment for accidentally exposed persons. Moreover, the early peripheral counts are less likely to be influenced by the infection and hemorrhage that may develop with progressive hematologic failure.

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LOCAL OBSTRUCTION OF THE INFERIOR VENA CAVA BY MASSIVE ASCITES*

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THE presence of a pressure gradient between the thoracic and abdominal portion of the inferior vena cava in cirrhotic patients with and without ascites and in patients with ascites of other origin has been described repeatedly.^{6-9,13-15} In most patients the pressure gradient occurred at the level of the diaphragm. In some of these patients inferior vena cavograms were performed which demonstrated localized narrowing of the inferior vena cava where it passes through the diaphragm. This narrowing was explained by either extrinsic compression from cirrhotic liver nodules,¹⁵ by deviation of the inferior vena cava from retraction of the liver,⁶ or by turbulent blood flow at the level of the transition from increased abdominal pressure to normal thoracic pressure, causing narrowing of the vessel at this point.¹³ During a routine examination of one patient with ascites, we recently found marked narrowing of the inferior vena cava at the level of the diaphragm and a pressure gradient at the same level, which prompted us to do this investigation.

METHODS

Five patients with massive ascites of noncirrhotic origin were examined. Inferior vena cavograms were made in supine position via a catheter introduced under local anesthesia from the femoral vein according to the Seldinger technique, before and after removal of the majority of the ascitic fluid. The pressure was recorded continuously during withdrawal of the catheter from the right atrium into the inferior vena cava. Pressures also were measured after selective catheterization of at least one hepatic vein in free and wedged position.

In 1 patient, the pressure in one renal vein was also determined.

In 7 large dogs, an identical procedure was performed under nembutal anesthesia, before and after injection of 2,000 to 3,000 cc. of physiologic saline solution into the peritoneal cavity and after removal of this fluid. In addition to the investigations in the patients, these dogs were examined not only in supine but also in erect position and venograms, as well as pressure measurements, were taken.

In 2 dogs, the circulating blood was replaced by saline solution. Immediately after cessation of the heart action, contrast material was injected into the inferior vena cava and roentgenograms were taken before and after injection of 2,500 cc. of saline solution into the peritoneal cavity.

RESULTS

In all 5 patients, a normal pressure was found in the right atrium of 2 to 5 mm. Hg, and, at withdrawal of the catheter into the inferior vena cava, a pressure gradient was recorded with an abrupt increase of the pressure to 15 to 20 mm. Hg at the level of the diaphragm. The pressure in the entire inferior vena cava was elevated with slightly higher measurements in the distal portion of this vessel. The free hepatic vein pressures equaled the figures for the inferior vena cava, while the wedged hepatic vein pressures measured 1 to 3 mm. Hg higher. After removal of most of the ascitic fluid, amounting to between 4,500 and 7,800 cc., the caval pressure fell to values 3 to 4 mm. Hg above the right atrial pressure with the free hepatic vein pressure at the same level and with wedged hepatic vein pressure also decreased, but 2 to 4 mm. Hg higher than

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the free hepatic vein pressure measurements.

Angiographically, a localized narrowing was seen of the inferior vena cava at the level of the diaphragm. The more distal portion of the inferior vena cava had a normal diameter and there was no evidence for generalized narrowing of this vessel. After paracentesis, the localized narrowing almost completely disappeared and the appearance of the caval vein was normal (Fig. 1, *A* and *B*). Selective contrast material injections into the hepatic vein demonstrated that veins entered the inferior vena cava just below the point of constriction.

These findings could be reduplicated in the dogs in supine position. A marked localized narrowing was noted of the inferior vena cava at the level where it penetrated the diaphragm with a pressure gradient between the supra- and infradiaphragmatic portion of the inferior vena cava, measuring 15 to 25 mm. Hg after the production of the artificial ascites. Before the injection of the fluid and after removal, the figures were normal (Fig. 2, *A*, *B* and *C*). Hepatic pres-

sure measurements were not taken. In the upright position, the ascites-induced pressure gradient disappeared and the constricted caval segment widened (Fig. 3, *A* and *B*). The roentgenograms demonstrated that a marked elevation of the diaphragm was present in the supine position, which decreased when the animal was placed in the erect position. In the 2 dead animals, a localized obstruction of the caval vein at the level of the diaphragm could be seen after introduction of fluid into the peritoneal cavity (Fig. 4, *A* and *B*).

DISCUSSION

The findings indicate that the narrowing of the inferior vena cava between the thoracic and abdominal portion of the inferior vena cava in ascites without liver cirrhosis is not caused by turbulent blood flow at the transition of two pressure systems because the narrowing could be reproduced in dead ascitic animals without flow in the caval vein. The roentgenograms in human beings and animals, however, raised the question whether the elevation of the diaphragms was related to the narrowing

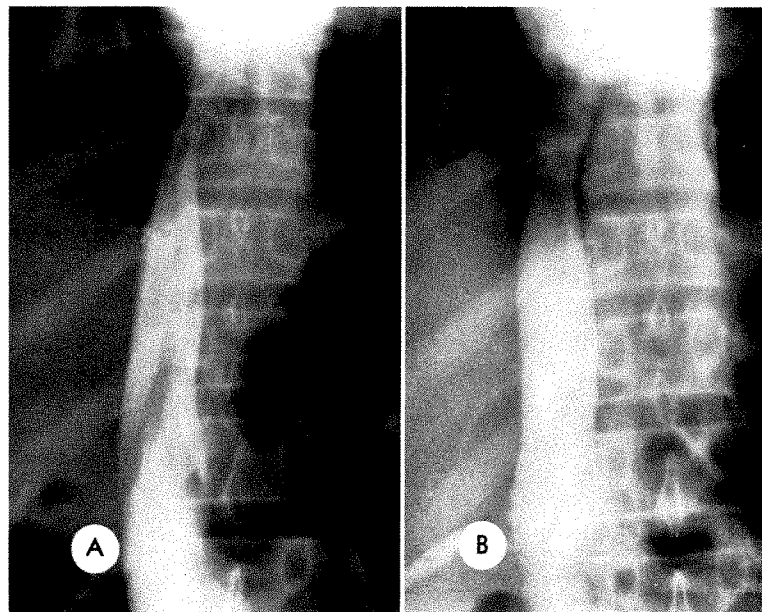


FIG. 1. Inferior vena cavogram in patient with tuberculous peritonitis (*A*) before, and (*B*) after removal of 5,200 cc. of ascitic fluid.

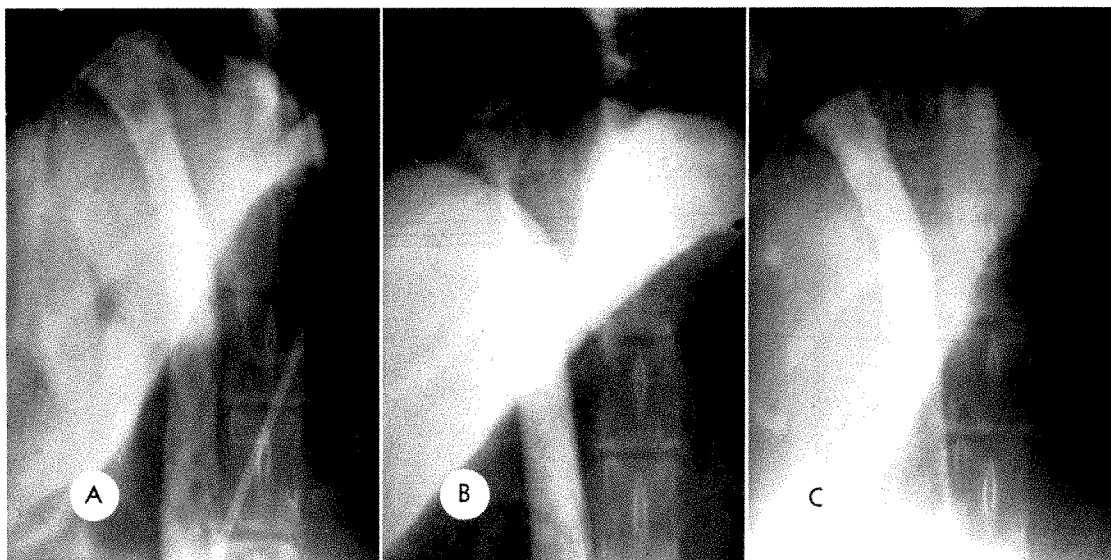


FIG. 2. Inferior vena cavogram in dog in supine position (*A*) before, (*B*) after injection of 2,500 cc. of saline solution into the peritoneal cavity, and (*C*) after removal of this fluid.

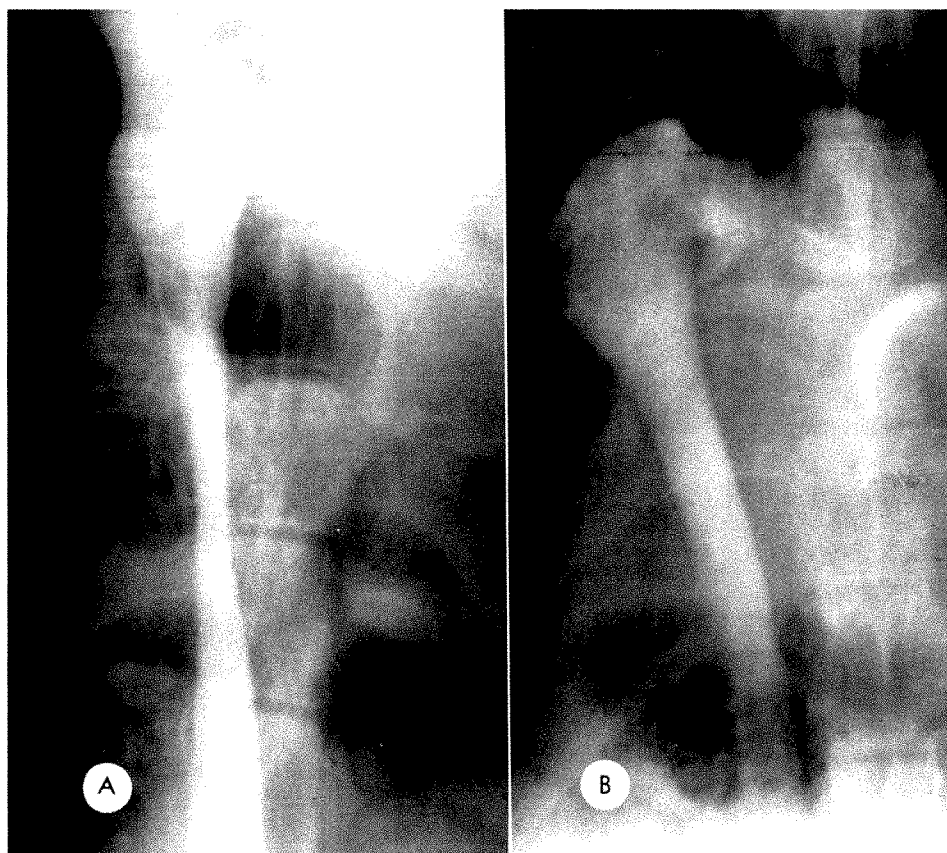


FIG. 3. Inferior vena cavogram in dog in (*A*) supine, and (*B*) upright position after injection of 3,000 cc. of saline solution into the peritoneal cavity.

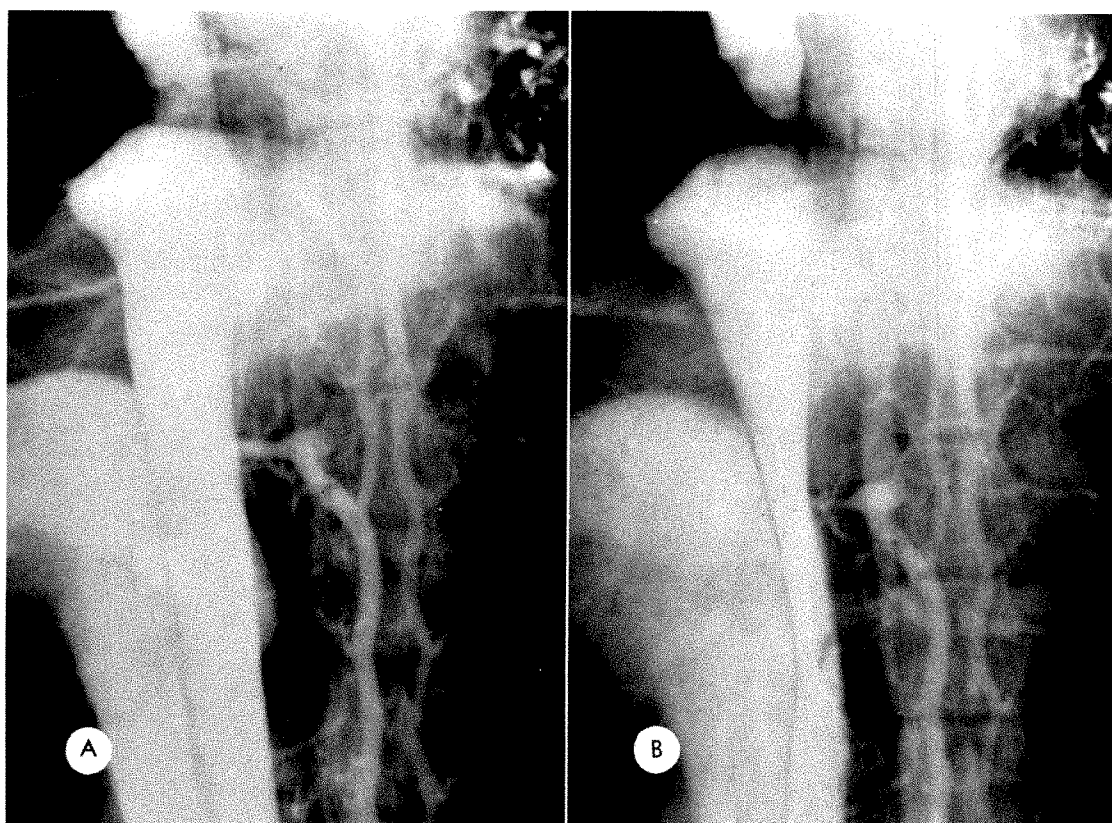


FIG. 4. Contrast material injection into inferior vena cava in dog shortly after the animal expired, (A) before and (B) after injection of 2,500 cc. of saline solution into the peritoneal cavity. The liver parenchyma is filled with contrast material and partially obscures the inferior vena cava.

of the vena cava and the pressure gradient. If the diaphragms were lowered by removal of the ascites or by placing the animal in the upright position, the caval narrowing and the pressure gradient disappeared. It is known that extreme contractions of the diaphragm, as, for instance, in the Valsalva maneuver, can produce changes in the diameter of the caval vein at the level of the diaphragm.¹¹ We, therefore, considered the possibility that the marked forced elevation of the diaphragm may have caused a similar narrowing of the vena cava. Mechanically, this is easily understandable. The right and left posterior crura which form the posterior and lateral margin of the foramen venae cavae are attached to the lumbosacral spine and are, therefore, firmly fixed in position. Pronounced elevation of the diaphragm places tension on the posterior crura, narrowing the orifice be-

tween them. We proved this by mechanical elevation of the diaphragm in 2 human cadavers which led to a marked narrowing of the foramen venae cavae.

The elevation of the free hepatic venous pressure is secondary to the elevated caval pressure.^{7,12} The minimal elevation of the wedged hepatic vein in relation to the free hepatic vein pressure is within normal limits. It indicates that the portal pressure is elevated by noncirrhotic ascites but that no gradient is present between the portal and caval system.

CONCLUSIONS

Massive ascites of noncirrhotic origin produces a localized narrowing of the inferior vena cava at the level of the diaphragm with a pressure gradient between the thoracic and abdominal portion of this vessel. Animal experiments support our im-

pression that this narrowing is a mechanical one produced by narrowing of the foramen venae cavae secondary to the marked elevation of the diaphragm. The caval narrowing, as well as the pressure gradient, disappears in dogs in the erect position. Further studies are planned to prove whether this is also true for human beings.

The elevated hepatic wedge pressure indicates elevation of the pressure in the portal system; however, the portal pressure is not significantly higher than the caval pressure and one cannot assume that the increased portal pressure produces a vicious circle, further increasing the amount of ascites.

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A PELVIC PHLEBOGRAM*

A CASE REPORT AND REVIEW OF THE LITERATURE

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ANORMAL phlebogram of the pudendo-vesico-presacral venous network was made accidentally during a retrograde pyelographic examination. We had not encountered a previous similar case, and a review of the literature disclosed no phlebographic demonstration of the entire pudendo-vesical plexus. The anatomy texts consulted failed to illustrate the details of the plexus of the prostate, urinary bladder, and presacral region. The present case offered a rare opportunity to study the comprehensive roentgen anatomy of this plexus, and it is, therefore, presented as a brief report.

REPORT OF A CASE

F.W., a 41 year old male, was admitted for the first time to the Durham VA Hospital in July, 1964 with the chief complaint of left flank pain for the past year. He had a history of removal of a left ureteral stone one year prior to admission. In December, 1963, an excretory urogram showed a left renal stone with associated mild left hydroneurter, and cystoscopy revealed a stricture of the distal left ureter. In the process of attempting to dilate the ureter, the bladder wall was perforated and a cystostomy was then performed. The bladder healed without complication. However, a bladder neck stricture was noted in February, 1964, and transurethral resection of the neck was done.

The major findings at this admission were left flank tenderness and many white blood cells in the urine. An excretory urogram showed a left calyceal stone and mild hydronephrosis, as well as nonvisualization of the distal left ureter. There was also stiffness of the left side of the bladder due to a scar from the previous injury. Retrograde pyelography was attempted under general anesthesia. It was difficult to identify the left ureteral orifice due to the scar. However, the orifice was seen, and a ureteral cath-

eter was inserted without evidence of resistance or bleeding. Because of hydronephrosis, 20 cc. of retrographin was introduced into the catheter and a roentgenogram was made immediately, resulting in the phlebogram of Figure 1. Intramural injection into the bladder wall was evident. No complication from the phlebography was noted. Three days after the phlebogram, a cystogram was made. The bladder shadow was identical to that of the previous pyelogram, and reflux of the opaque medium into the left ureter was noted. The patient was then discharged.

Roentgen Findings (Fig. 1). The ureteral catheter lay in the region of the left bladder wall where opaque medium residue was still present. The opaque medium had been absorbed and had drained into the pudendo-vesical plexus bilaterally. Also, the sacral plexus was opacified through communicating branches and back-

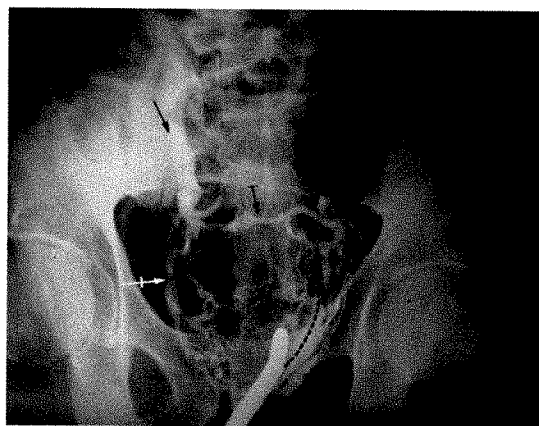


FIG. 1. Accidental injection of retrographin into the urinary bladder wall resulted in a normal male phlebogram of the pudendo-vesico-sacral plexus. Dotted line shows the position of the ureteral catheter from the cystoscope. →Hypogastric vein. ↔Presacral vein. ↔Lateral vesical vein. The presacral vein and lateral vesical veins form a heart-shaped circuit. The veins of the network are tortuous and irregular in caliber.

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flow. Veins emerging from the sacral foramen were noted. Some of the opaque medium had already emptied into both of the hypogastric veins. The right common iliac vein and inferior vena cava were faintly seen. The right and left lateral main channels of the pudendo-vesical plexus and a large transverse presacral vein formed a heart-shaped circuit. The apex of this circuit was located at the base of the prostate, where the deep dorsal vein of the penis drains. From this venous circuit, numerous branches were distributed to the prostate, bladder, pre-sacral tissue, and sacrum, forming a large unit of venous network. The veins of the network were tortuous and irregular in caliber.

DISCUSSION

This accidental roentgenogram (Fig. 1) demonstrated accurately the normal venous drainage of the prostate, urinary bladder, and presacral region. Santorini described the anterior venous network over the prostate and bladder neck region in 1724, and it is known as the plexus of Santorini. Batson⁶ and Beneventi and Noback⁷ studied the pudendo-vesical plexus, injecting colored water or vinylite solution into the veins of cadavers. Injection into the deep dorsal vein of the penis outlined three pudendo-vesical plexuses, the anterior Santorini plexus and each lateral plexus. These drain into the hypogastric vein. This network also communicates with the sacral veins. Batson described prostatic cancer metastasis through these venous channels. The roentgenogram in the present case confirms the results of their study. Many attempts have been made to demonstrate the pelvic venous drainage in the past. Pelvic phlebography by means of an opaque medium injection into the deep dorsal vein of the penis and of the clitoris was attempted in early 1950. It was possible to demonstrate the lateral vesical vein. However, this site of injection is not favorable for clinical use, and it has rarely been practiced. So far, intra-osseous pelvic phlebography has been the only method in clinical use. Judging from a review of the literature on pelvic phlebography and of the normal venous drainage of the male pelvis (Fig. 2), an intra-osseous pelvic phlebo-

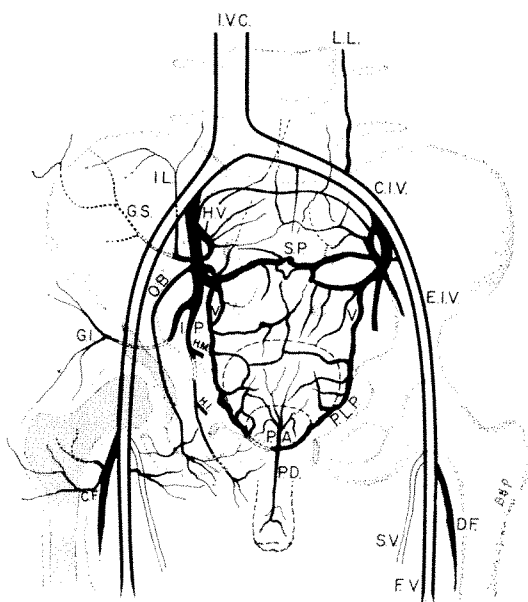


FIG. 2. This diagram of the normal male pelvic venous anatomy is based on various pelvic phlebograms appearing in the literature and the present case.

- C. F. —circumflex branch of femoral vein
- C. I. V. —common iliac vein
- D. F. —deep femoral vein
- E. I. V. —external iliac vein
- F. V. —femoral vein
- G. I. —inferior gluteal vein
- G. S. —superior gluteal vein
- H. I. —inferior hemorrhoidal vein
- H. M. —middle hemorrhoidal vein
- H. V. —hypogastric vein
- I. L. —ilio-lumbar vein
- I. P. —internal pudendal vein
- I. V. C. —inferior vena cava
- L. L. —lateral lumbar vein
- O. B. —obturator vein
- P. A. —anterior pudendo-vesical plexus (Santorini's plexus)
- P. L. P. —lateral pudendo-vesical plexus
- S. P. —presacral vein
- S. V. —greater saphenous vein
- V. —vesical vein

gram would only demonstrate the veins of the lateral pelvic wall in normal subjects.

Table 1 is a list of some of the phlebographic studies from the literature and the results obtained. It is interesting to note that most of the phlebograms showed back-flow into the sacral vein. This may explain frequent bony metastasis of pelvic tumors. The various phlebograms demonstrated the

TABLE I

Sites of Injection	Reference No.	Opacified Veins
Femoral trochanter	10,15,18	Obturator, inferior gluteal, iliac
Os pubis	2,10,14,18	Obturator
Os ischii	10	Internal pudendal, obturator, inferior gluteal
Sacrum	10	Sacral
Iliac crest	2,10,17	Superior gluteal, ilio-lumbar
Deep dorsal vein of penis	1,6,9,10,11	Prostatic, obturator, internal pudendal, lateral vesical
Deep dorsal vein of clitoris or corpus cavernosum clitoridis	15	
Paracervical region of uterus	10	Internal pudendal, obturator
Hemorrhoid	15	Vagino-uterine plexus, vesical vein
Ischial region, soft tissue	10	Superior hemorrhoidal, inferior mesenteric
Femoral vein with compression of inferior vena cava	15	Inferior gluteal, internal pudendal obturator
	2,4,6,12,15	Proximal hypogastric, sacral and presacral plexus, vertebral vein

veins of the lateral pelvis but not of the entire pudendo-vesical plexus. At present, there is no proper method of performing a phlebography to visualize the pelvic visceral veins adequately.

CONCLUSION

The roentgenographic aspects of the normal pelvic venous drainage in the male are described on the basis of a phlebogram of a case demonstrating the entire pudendo-vesical plexus, and various other reports of pelvic phlebographic studies from the literature are reviewed.

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HIGH KILOVOLTAGE PELVIMETRY*

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THE lack of a uniformly accepted technique for performing pelvimetry is indicated by the many different methods described in the literature and used today.⁶ Triangulation,⁴ parallax,² differential divergent distortion,⁵ stereoscopy,^{7,9} and isometry⁸ are utilized by various authors. With one exception,¹ the radiation exposure to the fetus or maternal gonads has not been recorded in any of these communications.

A technique for pelvimetry should be simple, accurate, and quickly performed. The radiation hazard to the mother and fetus must represent the least possible dose. The elimination of correction rulers and magnification tables would expedite interpretation of the roentgenograms.³ In this paper a high kilovoltage pelvimetry technique which meets all of the above requirements is described. The radiation dose to the maternal pelvis using the high kilovoltage technique is measured and compared with conventional kilovoltage technique.

METHOD AND MATERIALS

One hundred and fifty kilovoltage radiation from a three phase generator was utilized at a target-film distance of 10 feet. High speed film was used in a high speed grid-cassette. The 8:1 grid was non-focused and had 100 lines per inch. The 1 mm. focal spot was used. Anteroposterior and lateral roentgenograms were taken with the patient standing against the cassette. There was no air gap between the patient and the cassette. The roentgen-ray tube was centered on the anterosuperior iliac spines for both views and was angled 20 degrees towards the feet for the anteroposterior roentgenograms.

Differential divergent distortion⁵ has been used at the Mallinckrodt Institute of Radiology for pelvimetry for many years. This method served as the conventional kilovoltage comparison of all measurements.

Initial measurements and comparison of the radiation exposure to the fetus and maternal pelvis were made using a pelvic phantom.* This phantom (Fig. 1*A*) was made of tissue equivalent material and contained the bony pelvis and upper femurs. Similar determinations were then made in 3 patients. All dosimeter measurements of the pelvic phantom or patients were made using a roentgenographic technique that produced diagnostic roentgenograms (Fig. 1, *B* and *C*).

Radiation exposure was measured with a dosimeter having a 0 to 200 mr range. The chamber was placed in the vagina of the phantom or patient, and a diagnostic roentgenogram was made. The chamber was read and recharged after each exposure. In the phantom, 6 separate exposures and readings were made for each view, and the average of these 6 readings was recorded in mr.

RESULTS

Table 1 shows the technical factors used for the different diagnostic exposures and the average mr recorded by the dosimeter. The average dose to the mid-pelvis of the phantom was 19 times greater with the 3 film conventional kilovoltage technique than with the 2 film high kilovoltage technique. The average dose recorded by the dosimeter placed in the vagina of patients is also given in Table 1. The conventional kilovoltage technique averaged a

* Picker-Alderson pelvic phantom, Model B, Serial No. 110.

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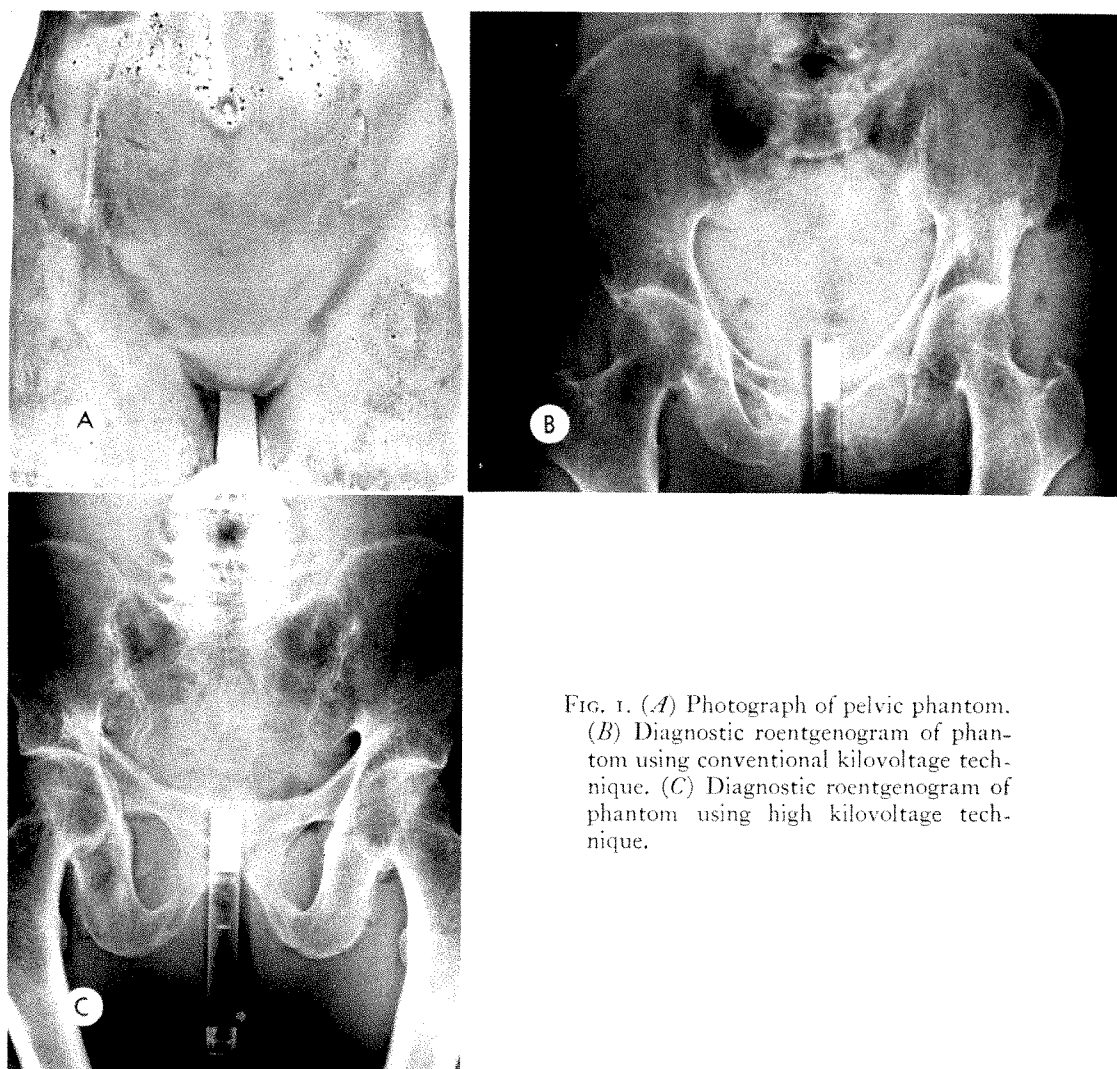


FIG. 1. (A) Photograph of pelvic phantom. (B) Diagnostic roentgenogram of phantom using conventional kilovoltage technique. (C) Diagnostic roentgenogram of phantom using high kilovoltage technique.

TABLE I

TECHNIQUES AND MILLIROENTGENS OF EXPOSURE IN VAGINA OF PELVIC PHANTOM AND PATIENTS

	Roentgenographic View	Target-Film Distance (inches)	Pelvic Phantom			Patients		
			mas.	kv.	Average mr Recorded in Vagina	Average mas.	Average kv.	Average mr Recorded in Vagina
Conventional Kilovoltage Technique	Anteroposterior	25	35	70	110	100	88	350
	Anteroposterior	40	60	70	90	150	88	280
	Lateral	36	80	70	50	350	96	390
High Kilovoltage Technique	Anteroposterior	120	1½	150	5	45	150	25
	Lateral	120	3	150	8	50	150	35

total of 1,020 mr to the mid-pelvis, while the high kilovoltage technique averaged a total of 60 mr to the mid-pelvis. Thus, the radiation hazard to the mid-pelvis was 17 times less with the high kilovoltage technique.

To test the accuracy of the high kilovoltage technique, comparison measurements using the 2 methods of pelvimetry were made on older patients. These results are tabulated in Table II. One skeletonized pelvis (Case 5) was roentgenographed, and the two techniques gave nearly identical results as compared with the true measure-

ments of this pelvis. No matter which technique was used, the bony landmarks were difficult to identify on some roentgenograms. This was particularly true of the ischial spines and, on conventional kilovoltage roentgenograms, of the pubic symphysis. In spite of these difficulties, the 2 techniques gave very similar measurements. The greatest disparity, between measurements was 5 mm., and this occurred only twice.

The distance from the ischial spines to the skin of the buttocks on lateral roentgenograms taken at 10 feet was found to

TABLE II
COMPARATIVE ACCURACY OF CONVENTIONAL KILOVOLTAGE AND HIGH KILOVOLTAGE PELVIMETRY
TECHNIQUES IN EVALUATING OBSTETRICAL MEASUREMENTS

Case No.	Anteroposterior Roentgenograms				Lateral Roentgenograms			
	Pelvic Inlet		Mid-Pelvis		Pelvic Inlet		Mid-Pelvis	
	High Kilovoltage Technique (cm.)	Conventional Kilovoltage Technique (cm.)	High Kilovoltage Technique (cm.)	Conventional Kilovoltage Technique (cm.)	High Kilovoltage Technique (cm.)	Conventional Kilovoltage Technique (cm.)	High Kilovoltage Technique (cm.)	Conventional Kilovoltage Technique (cm.)
1	14.4	14.3	10.5	10.5				
2	13.5	13.3	10.1	10.3				
3	13.3	12.8	10.4	10.7				
4	12.3	12.4	10.8	11.2	11.3	11.1	12.9	13.0
5	(12.5) 12.5	12.6	(8.8) 8.9	9.0	(10.1) 10.0	10.2	(10.9) 11.0	11.1
6	11.2	11.1	7.6	7.9	9.6	9.3	9.1	9.2
7	13.3	12.9	9.0	8.8	10.6	10.6	12.3	11.8
8	14.3	14.4	11.3	11.2	12.2	12.4	13.1	13.5
9	13.6	13.2	10.7	10.9	11.5	11.4	11.9	11.6
10	14.8	14.6	10.3	10.1	14.2	14.0	13.3	13.0
11	13.9	13.6	10.0	9.9	13.4	13.0	13.3	13.4
12	12.9	12.7	10.4	10.1	10.5	10.4	12.4	12.2

Note: Eleven older patients and 1 skeletonized pelvis (Case 5) were studied. In Case 5, numbers in parentheses represent true diameters.

vary normally from 8 to 14 cm. By using equilateral triangles, the greatest magnification error of the interspinous diameter was approximately 5 per cent, or in the average human pelvis, about 5 mm. However, if all ischial spines are at least 8 cm. from the cassette in the anteroposterior projection, a 3 per cent reduction of the measured diameter can arbitrarily be made. Therefore, the possible error in the final determination of a pelvic obstetrical diameter is plus or minus 1 per cent. This is well within acceptable limits for clinical use. The same magnitude of error (plus or minus 1 per cent) was present in the other pelvic measurements.

DISCUSSION

High kilovoltage pelvimetry is technically simple. Special cassette holders or tube shifts are not required. Also, the roentgenographic equipment does not have to be modified.⁴ If a three phase generator is not available, or if a 10 foot target-film distance cannot be obtained, a medium energy

radiation therapy unit in a moderate sized room frequently can be used.³

Radiation scatter and hazard are minimized and image detail is enhanced by using the smallest possible field and a good collimator. An air gap, as frequently used in high kilovoltage chest roentgenography, was not used in order to minimize magnification. This required the use of a grid with a high degree of scatter clean-up. A 16:1 non-focused grid will give slightly better detail (clean-up) than the 8:1 grid now used. However, the radiation hazard to the patient will also be increased by the 16:1 grid. Image detail is increased by using the small focal spot.

The radiation hazard to the mother and fetus has become a serious problem in recent years. Whitehouse *et al.*¹⁰ have emphasized the need for decreasing the radiation dose to the maternal pelvis so that only the minimum possible dose is received. The high kilovoltage technique reduces the radiation exposure to the maternal mid-pelvis and fetus significantly (Table 1).

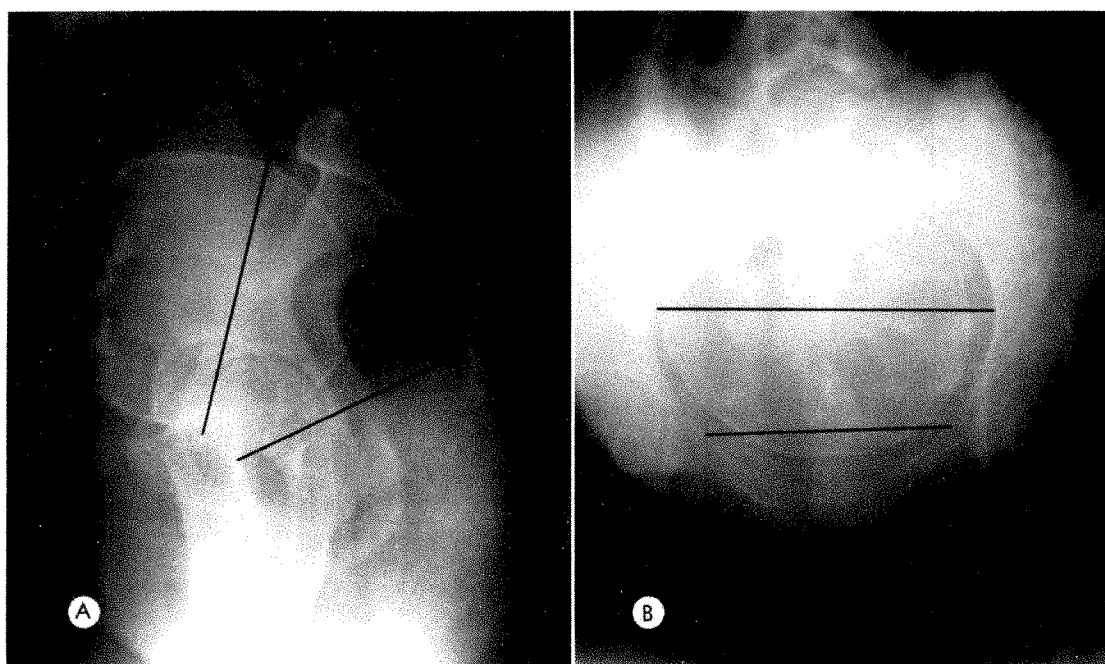


FIG. 2. (A and B) Lateral and anteroposterior high kilovoltage pelvimetry roentgenograms demonstrate the different obstetrical diameters.

Only 2 views should be used in any method and just the maternal pelvis and fetal head should be roentgenographed. All of the previously described methods of pelvimetry, except the isometric method when used alone, require at least 3 roentgenograms.

By using a high kilovoltage technique, only 2 films are required for a complete examination. At a target-film distance of 10 feet, the roentgen rays are very nearly parallel, and the magnification error can be reduced to plus or minus 1 per cent. Magnification correction devices are not required and the different obstetrical measurements are made directly from the 2 roentgenograms. All pelvic diameters measured on roentgenograms using the conventional kilovoltage technique can also be determined on the 2 high kilovoltage roentgenograms (Fig. 2, *A* and *B*). By centering the tube on the anterosuperior iliac spines and angling the roentgen-ray beam 20 degrees towards the feet, the ischial spines are usually projected into the pelvis. The anatomic configuration of the entire pelvic inlet also is well demonstrated. The size and position of the fetal head are determined easily. The upright roentgenograms give the most reliable evaluation of the fetal head and its relationship to the maternal pelvis.

SUMMARY

A high kilovoltage pelvimetry technique is described and compared with a conventional kilovoltage technique. One hundred and fifty kilovoltage radiation at a target-film distance of 10 feet was utilized. High speed film was employed in a high speed, 8:1, non-focused, grid cassette. The radiation dose to the mid-pelvis was measured in a phantom and in patients. The obstetrical diameters obtained by the 2 techniques were compared. The maximum roentgenographic magnification error occurring with

the high kilovoltage technique was 5 per cent, and this error is reduced to plus or minus 1 per cent by making a 3 per cent correction of the measured diameter.

The high kilovoltage technique is the method of choice for pelvimetry. The radiation dose to the maternal pelvis and fetus is reduced 17 times. Magnification factors and correction devices are not required, and all obstetrical measurements are made directly on the 2 upright roentgenograms.

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INTRAVENOUS PLACENTOGRAPHY*

A CRITICAL ANALYSIS OF 85 CASES

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THE need for a safe and dependable means of placental localization in third trimester bleeding is generally acknowledged, and one or another of several kinds of radiologic examinations have generally been employed to obtain such information. The demonstration of increased thickness of the uterine wall may define the site of placental implantation,^{6,17} and displacement of the fetal head from the symphysis or sacral promontory is used as a sign of low implantation in gravitational placentography.^{1,13} Roentgenographic evidence of placental calcification has been a disappointing means of localization in our hands, despite the finding of such calcification in 30 per cent of placentas after 36 weeks of gestation in one series.¹¹ The introduction of either negative or positive contrast material into the urinary bladder has facilitated localization of the placental implantation site; emphasis is placed upon the demonstration of a thick homogeneous density between the presenting part and the margin of the bladder.¹⁸

Isotope localization of the placenta was first reported in 1951 using radioactive sodium.³ Radioactive iodinated^{14,20} and, more recently, chromium labelled¹⁵ human serum albumin have also been used. The maximum radiation dose to mother and fetus has been calculated to be in the range of 50 to 70 mr.^{14,19}

Opacification of the placenta itself was first described by dos Santos⁷ in 1929 in a series of translumbar aortograms of which one was performed on a woman in the sixth month of pregnancy. Others have utilized this technique,^{5,12} but it has not gained wide popularity. The retrograde femoral catheter approach to uterine arteriography

and placentography has been explored^{2,10} and produces excellent opacification of the placental sinusoids.

Ezes *et al.*⁸ described an intravenous method of placentography in 1956, and Goodlin *et al.*,⁹ Coale *et al.*,⁴ and Richey¹⁶ in this country have elaborated on this technique. Since 1961, intravenous placentography has been the chief means of placental localization used at the University of Texas Medical Branch Hospitals, and this communication reports our results with this technique.

PROCEDURE AND INTERPRETATION

The technique of intravenous placentography consists of the rapid intravenous injection of a large bolus of iodinated contrast material, the amount determined by the weight of the patient, followed by abdominal roentgenography. After exposure of an anteroposterior scout roentgenogram of the abdomen, the patient is tested for iodine sensitivity with a small intravenous injection of renovist, the contrast agent we have used almost exclusively. The arm-to-tongue circulation time is determined (using decholin), following which the preliminary roentgenogram is inspected and necessary adjustments in positioning and technique are made. A syringe with a 100 cc. capacity is then loaded with contrast material (80 cc. for body weight less than 125 pounds, 90 cc. for 125 to 150 pounds, and 100 cc. for over 150 pounds) and connected to a 10 or 12 gauge Robb-Steinberg cannula which has been placed in an antecubital vein by cut-down. The bolus of contrast material is injected rapidly by hand (requiring about 2 seconds), and a single supine anteroposterior roentgenogram of

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the abdomen is exposed 2 seconds after the circulation time, counting from the end of the injection of contrast material. Thus, if the circulation time was found to be 10 seconds, the film exposure would be made 12 seconds from the end of the injection. The exposure time has been fixed at 1 second, the other technical factors being varied as necessary to obtain a technically satisfactory roentgenogram. The roentgenogram so obtained is inspected immediately and compared with the preliminary scout roentgenogram. If the placental sinusoids are opacified and the placenta thus located, the examination is terminated. If for any reason the roentgenogram does not show the location of the placenta (exposure too early or too late, for example), we have not hesitated to repeat the injection and roentgenography, provided, of course, that the condition of the patient permits it.

Localization of the placenta by this method depends upon opacification of the placental sinusoids. They appear as rounded poorly circumscribed opacities 1 to 2 cm. in diameter having very much the appearance of cotton balls. When the patient's bowel is relatively empty and gas and fecal shadows do not interfere, the placental sinusoids are easy to locate, and the diagnosis of site of implantation may be reliably made. It is particularly easy to localize the placenta when it is seen tangentially, from the side, as when it is located in the fundus or on the right or left uterine wall. When it is located on the anterior or posterior wall, there is less superimposition of opacified sinusoids, and, while the location of the placenta is somewhat more difficult in this circumstance, it may still be seen with relative ease. When the placenta is normally implanted, it will usually but not always be found opposite the fetal abdomen, and the fetal head (in a vertex presentation) will ordinarily be symmetrically situated in the maternal pelvis (Fig. 1, *A* and *B*).

In marginal (partial) placenta previa or low-lying placenta (without encroachment

upon the cervical os), the placental sinusoids will be seen to be located in closer proximity to the presenting fetal part, and the fetal head (or buttocks in a breech presentation) is apt to be deviated to the side opposite the placenta (Fig. 2, *A* and *B*). In our experience it has been impossible to differentiate between marginal placenta previa and low-lying placenta by intravenous placentography, and we have erred in both directions, both over- and under-diagnosing this abnormality when the placenta was implanted in a lower than normal position. We ordinarily report "low-lying or marginal placenta" under such circumstances, and, alerted to the possibility of placenta previa, the referring obstetrician may elect to perform a cautious pelvic examination. If the placenta is not palpated, the patient may be permitted to go into labor spontaneously and possibly to deliver from below, there being no other indication to the contrary. It should be remembered, however, that a low-lying placenta may become a partial placenta previa as the cervical os dilates.

Placenta previa centralis ordinarily poses no problem. In the typical case the placental sinusoids are clearly seen inferior to the fetal presenting part and between the presenting part and the pubic symphysis (Fig. 3, *A* and *B*). A low-lying placenta on the anterior or posterior uterine wall may simulate central placenta previa; however, the placental sinusoids in such a case will be seen to be mainly superimposed on the fetal head (assuming a vertex presentation) in the anteroposterior projection, and the fetal head will likely be located deeply and symmetrically in the maternal pelvis. With central placenta previa, the fetal head is apt to be located high and to one side, and the placental sinusoids will be seen between the fetal head and the maternal bladder and not superimposed upon the head.

Before interpretation is attempted, the adequacy of the examination should be appraised. If the roentgenogram made following the contrast injection is exposed too soon, it will show contrast material in the

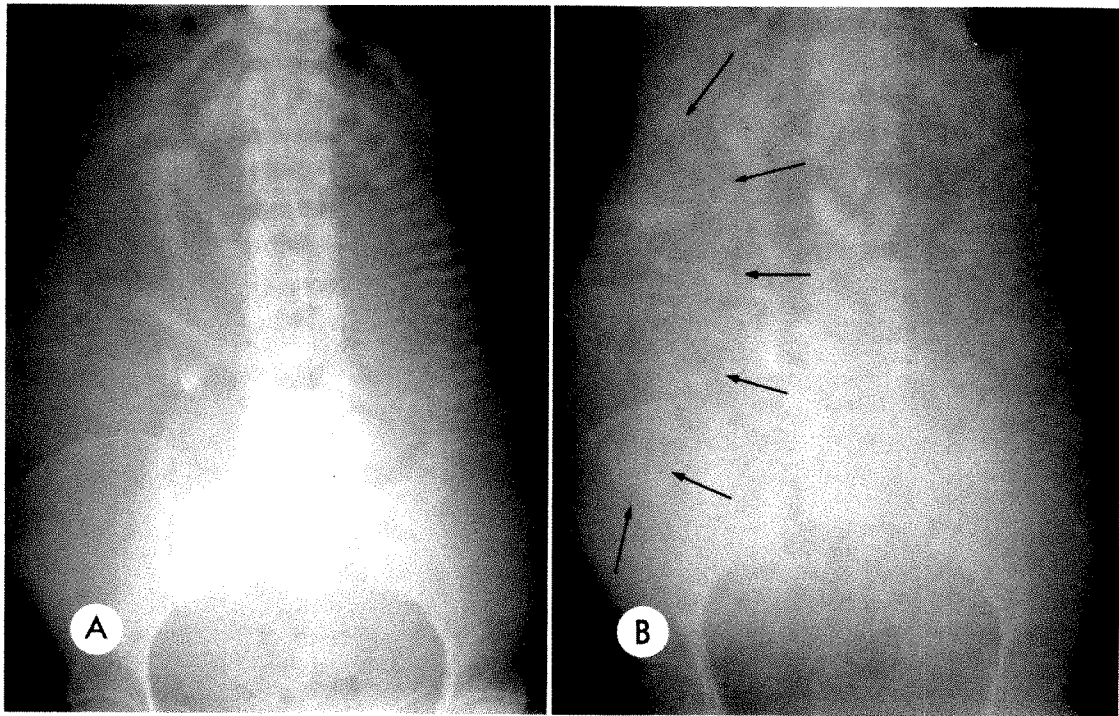
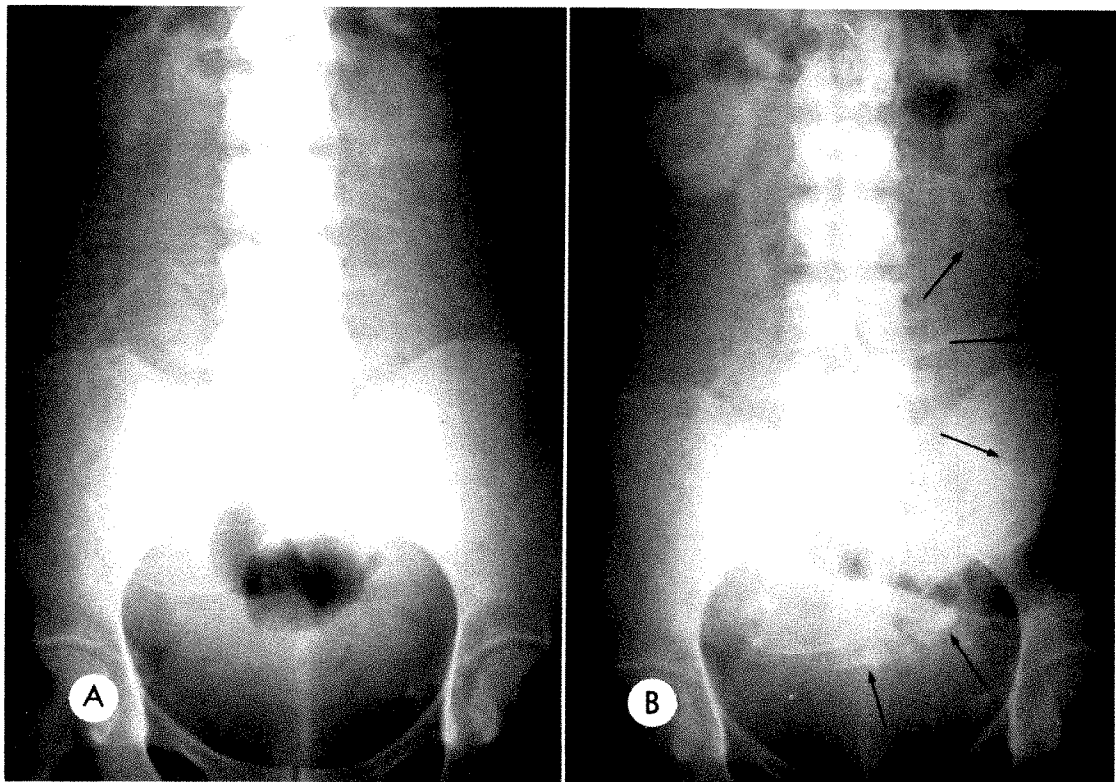


FIG. 1. Normal implantation of the placenta. (A) Preliminary roentgenogram shows a single fetus presenting by the vertex. (B) Roentgenogram made following injection of the contrast material. The placenta is located on the right side of the uterus (arrows) as determined by opacification of the placental sinusoids.



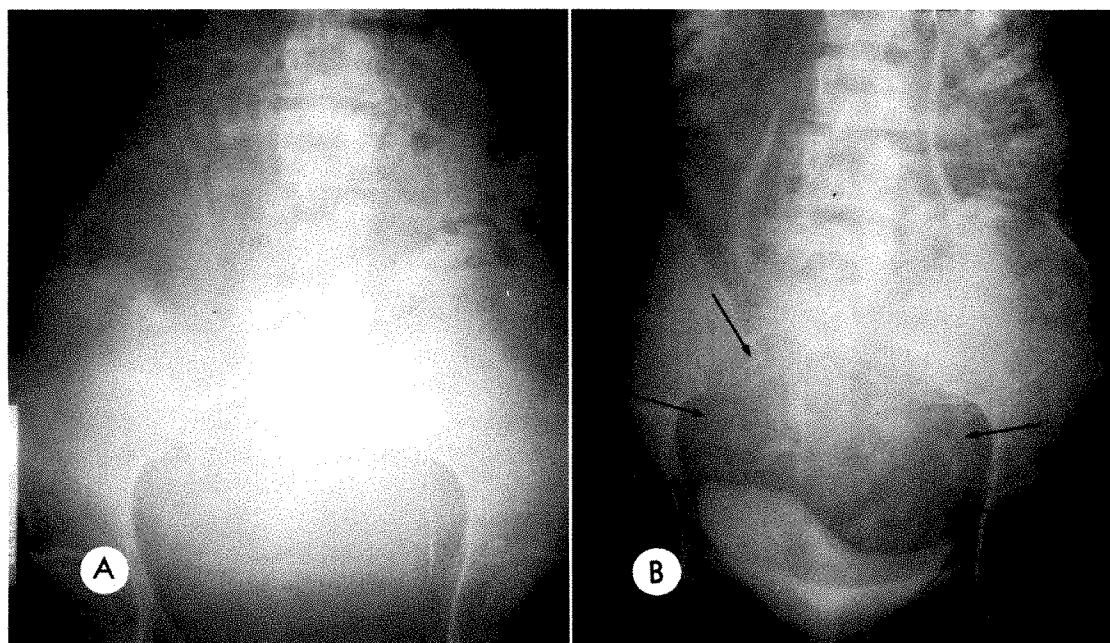


FIG. 3. Central placenta previa. (A) Roentgenogram prior to injection of the contrast material shows the fetus in a transverse lie, the head in the left iliac fossa. (B) Roentgenogram made following a second injection of contrast material (the roentgenogram following the first injection was unsatisfactory). The ureters and bladder are opacified from the first contrast injection. The placental sinusoids (arrows) were rendered opaque by the second injection. The placenta is located between the fetal head and the maternal bladder.

abdominal aorta and pelvic arteries (the dilated and very tortuous placental arteries may be seen; they are a less reliable indicator of the location of the placenta than the placental sinusoids). If the roentgenogram is exposed too late, no contrast material will be seen in the arteries, veins or placental sinusoids. If properly exposed, the femoral arteries may be outlined faintly by a small residue of contrast material, and the placental sinusoids will be well seen. A dense bilateral nephrogram will regularly be seen if the roentgenogram is exposed at or near the circulation time.

The examination is more pictorially elegant and the diagnosis easier to secure in thin subjects. Obesity is itself no contraindication, however, and we have successfully performed intravenous placentogra-

phy on a 330 pound patient nearly at term with the resulting placental opacification being adequate for the purpose of accurate localization.

MATERIAL AND INDICATIONS

One hundred and seventeen patients were examined between January, 1961, and July, 1964, and 106 are reported here. Information on delivery was unavailable in 11 cases, and these were omitted. There were 6,792 deliveries during this period; intravenous placentography was performed on 1.7 per cent of these cases.

The commonest indication was third trimester bleeding, usually painless, but pain was the complaint in 16 patients. Some asymptomatic patients who had previously had cesarean sections were examined in



FIG. 2. Marginal implantation of the placenta. (A) Preliminary roentgenogram shows a single fetus presenting by the vertex. The fetal head is in the right iliac fossa and high above the symphysis. (B) Roentgenogram made following injection of the contrast material shows opacification of the placental sinusoids and localizes the placenta to the lateral wall and lower uterine segment on the left.

order to localize the placenta prior to repeat cesarean section. Other indications included persistent transverse lie and suspected abdominal pregnancy.

Of these 106 cases, 85 were considered satisfactory for interpretation, an unsatisfactory rate of 20 per cent. Many of these unsatisfactory studies were obtained early in our experience with the technique, and only 4 of the last 40 cases proved unsatisfactory for interpretation (10 per cent). Reasons for unsatisfactory studies (not interpretable) included the following: roentgenogram exposed too early or too late; poor roentgenographic technique; motion of the patient during the film exposure; and fetal death with placental nonfunction.

RESULTS

The site of implantation of the placenta was correctly localized by intravenous placentography in 81 of the 85 cases for an over-all accuracy of 95 per cent. Seventy of 72 normally implanted placentas were correctly localized, an accuracy of 97 per cent. The diagnosis of placenta previa was established by vaginal examination or by inspection and palpation at the time of cesarean section. Placenta previa was confirmed in 13 of the 85 cases, 8 times by cesarean section and 5 times by vaginal examination, an incidence in this series of 15.3 per cent. Eleven of 13 abnormally located placentas were correctly diagnosed as placenta previa or low implantation

of the placenta, an accuracy of 85 per cent. There were 2 false positives (incorrect diagnosis of placenta previa) and 2 false negatives (failure to detect placenta previa). One of the false negatives showed partial infarction of the placenta on pathological examination, perhaps explaining why it abnormal location was not detected angiographically.

Analysis of Table I will show other differences between the group of 13 patients with verified placenta previa and the 72 patients with normal placental implantation. In general, more injections and a large volume of contrast material were required to make a diagnosis of placenta previa.

HAZARDS AND REACTIONS

There were no serious reactions to the contrast material or the procedure, and there were no differences in number or kind of reactions between patients with and without placenta previa or between patients with one or two contrast injections. A feeling of warmth was regularly experienced following the injection of the contrast agent, and this lasted 20 to 30 seconds in most instances. It did not interfere with the patient's ability to cooperate in the great majority of cases. An occasional patient complained of nausea, and a few vomited. Other minor reactions included headache and cough. None required treatment and all passed quickly. Each patient was premedicated with 25 to 50 mg. of phenegran routinely; the part which this

TABLE I
COMPARISON OF PATIENTS WITH PLACENTA PREVIA AND NORMAL IMPLANTATION

	Placenta Previa	Normal Implantation
Average No. of Injections	1.20	1.11
Average Amount of Contrast Material	111.2 cc.	99.2 cc.
Average Birth Weight of Fetus	5 lb. 10 oz.	6 lb. 7 oz.
Average Maternal Hemoglobin	10.4 gm. %	11.3 gm. %
Average Maternal Weight	143.8 lb.	153.6 lb.
Average No. of Weeks Pregnant	33.1	33.6
Average Age	27.7 years	25.7 years
Average Gravidity	5.8 pregnancies	4.3 pregnancies
Average Parity	4.0 babies	3.7 babies

may have played in the prevention of serious reactions is uncertain.

There were 7 fetal deaths in this series of 106 cases. In no case was the procedure of intravenous placentography incriminated or seriously considered as directly related to the fatal outcome. In most cases fetal death was thought to be due to an abnormality, the symptoms of which prompted the performance of placentography (marginal sinus rupture, abruptio placentae, etc.). In 1 case death was thought to be related to a prolapsed cord, and death in 2 cases followed abdominal pregnancy.

The radiation dose was monitored in several cases by the placement of ionization chambers of the Laughlin or Baldwin-Farmer type in the rectum during the exposure of the two films ordinarily required. This dosage may be considered to approximate the radiation dosage to the maternal gonads. The dose averaged 340 mr in 5 patients in whom 1 injection of contrast material was made and 2 anteroposterior roentgenograms of the abdomen were obtained. The dose to the fetal gonads can be expected to be somewhat higher.

CONCLUSIONS

The choice of a method for placental localization should take into consideration several factors, including ready availability at all hours, ease of performance, hazard to mother and fetus, radiation dosage, and reliability of interpretation. Our choice of intravenous placentography is based upon the following considerations.

The intravenous method produces an image of the opacified placental sinusoids which is less distinct and less dense than that obtained with retrograde femoral catheter aortography, but the hazards and complications of arterial puncture are avoided and the roentgenograms obtained are interpretable in 90 per cent of the cases. The intravenous method requires the injection of contrast material to localize the placenta while soft tissue and gravitational placentographies do not, but no lateral roentgenogram is required with the intra-

venous method, and placental structures themselves are opacified, allowing accurate direct visual localization of the placenta rather than estimation of its position from displacement of other structures. Radiation dosage to mother and fetus are greater with the intravenous method than with isotope localization, but scanners are not yet standard equipment in most hospitals and offices, and the visual representation of the placenta on roentgenograms inspires more confidence than a comparison of uptakes in different parts of the uterus expressed as numbers. Of all the alternate methods of examination, isotope localization seems to us the most promising, and a study is now under way to directly compare the results of intravenous and isotope placentography (using chromium labelled red blood cells).

SUMMARY

One hundred and six patients were examined for placental localization by intravenous placentography, and 85 satisfactory cases are analyzed.

Over-all accuracy in placental localization was 95 per cent; the examination failed in the detection of 2 of 13 cases of placenta previa, and 2 of 72 patients with no placental abnormality were thought to have abnormal implantation sites.

The examination proved to be a safe and effective means of localization of the placenta, acceptable to both patients and referring physicians.

The technique of the procedure is outlined and comparisons between patients with and without placenta previa are summarized.

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RADIOISOTOPIC LOCALIZATION OF THE OVERACTIVE HUMAN PARATHYROID*

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ALTHOUGH there is little question of the desirability of identifying and localizing abnormal parathyroid glands before surgery, existing methods for accomplishing these ends either lack precision or do not have the potential to assess function directly. The possibility of employing external radioisotope scanning for this purpose has hitherto not been exploited, although the method has been used to advantage in the evaluation of other endocrine and exocrine gland pathology.^{1,2}

There are two basic requirements in the application of external scanning to the identification of parathyroid tissue. First, the isotope used must emit radiation of the proper energy to allow for adequate resolution by an external detector. Second, the isotope should be sufficiently localized in parathyroid tissue so that the radioactivity in surrounding tissues does not interfere with the determination.

Since the parathyroid glands synthesize and elaborate a polypeptide hormone,³ the use of a radioactive amino acid precursor label is a logical one. Unfortunately, the common carbon 14, sulfur 35 and hydrogen 3 labeled amino acids are not suitable for external counting. On the other hand, the Se⁷⁵ labeled amino acid analogue of methionine, selenomethionine, in which there is an isomorphous substitution of selenium for the naturally occurring sulfur, can be used for this purpose. Selenium 75 emits gamma radiation of 0.27 mev. and has a half-life of 127 days. In its tissue penetrability and collimation requirements, its radiation is sufficiently comparable to the 0.36 mev. gamma of iodine 131 so that the same equipment can be used for both isotopes.

Tritiated methionine has been successfully employed to evaluate abnormalities in protein synthesis by pancreatic tissue.³

This report is concerned with the use of selenomethionine as a parathyroid label and with its utilization for the clinical localization of abnormally-functioning parathyroid tissue.

ANIMAL STUDIES

The uptake of methionine by the rat parathyroid and surrounding tissue was investigated as a prelude to the human studies.⁵ Sprague-Dawley, white, female rats were kept on a low calcium diet for 2 weeks to stimulate parathyroid activity. In addition, the animals received, on alternate days, 6 subcutaneous injections of thyroxine, 20 µg. each, to suppress thyroid protein anabolism. The day following the last injection of thyroxine, tritiated methionine was administered intravenously into the inferior vena cava. The doses ranged from 250 to 1,000 µc. Animals were sacrificed at intervals from 5 minutes to 1 hour following injection. The parathyroids and surrounding tissue were removed and fixed in acetone to prevent the leaching of parathyroid polypeptides. Radioautographs were prepared by the dipping emulsion technique.⁴

Figure 1, *A* and *B* shows radioautographs of parathyroid, thyroid and muscle tissue taken 10 minutes following the injection of 250 µc of tritiated methionine. Silver grains are quite evident over the parathyroid cells. The thyroid colloid shows no evidence of radioactivity and there are only a few grains visible over the thyroid cells and muscle.

It is clear from these experiments that

* Presented at the Twelfth Annual Meeting of the Association of University Radiologists, Chicago, Illinois, May 14-16, 1964. From the Harvard Medical School Department of Radiology at the Peter Bent Brigham Hospital.

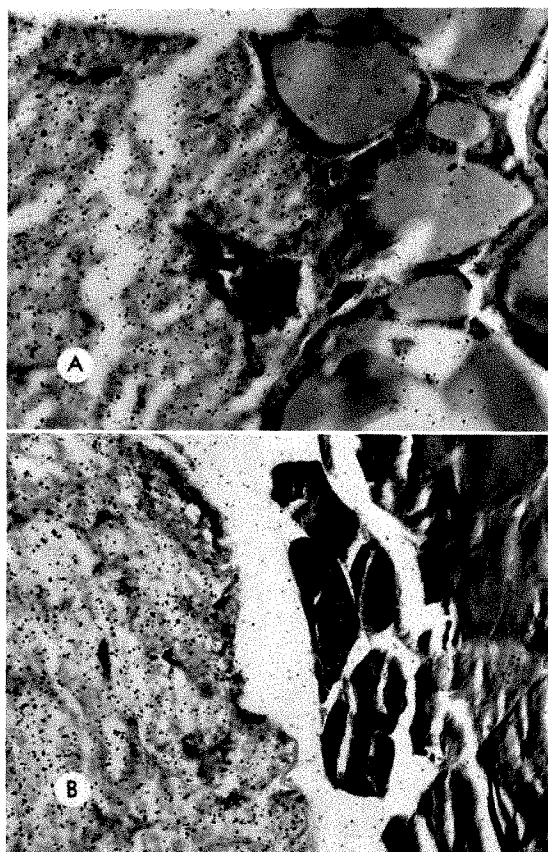


FIG. 1. Radioautographs of rat parathyroid gland, Cason stain. Tissues were removed and fixed in acetone 10 minutes after injection of tritiated methionine. (A) Parathyroid (left) and thyroid. (B) Parathyroid (left) and muscle. A greater number of silver grains is visible over parathyroid than over other tissues (500X magnification).

methionine can be used to tag hyperactive parathyroid specifically, in contrast to surrounding muscle and thyroxine-suppressed thyroid tissue.

HUMAN PHYSIOLOGIC INVESTIGATIONS

After the concentration of methionine by the hyperactive rat parathyroid was demonstrated, the distribution of selenomethionine was studied in a patient suffering from overt hyperparathyroidism.

CASE STUDY

ED (PBBH No. 2-38-03), a 41 year old woman, had two renal calculi removed 5 years before her admission. Two years previously she

had delivered a full term infant who suffered from neonatal tetany; the patient's calcium at that time was 9.3 mEq./L. On admission to the hospital she complained of anorexia, irritability, constipation, polyuria, polydypsia and bone pain. On physical examination a 2X3 cm. nodule was palpable at the left lower thyroid lobe. Calcium was 9.0 mEq./L., phosphorus 1.5 mM., alkaline phosphatase 4.0 Bessy Lowry units, and blood urea nitrogen 33 mg. per cent. On a 200 mg. calcium diet, 400 to 600 mg. of calcium was found in her daily urine. The patient was given cytomel, 50 µg. every 12 hours, for 2 days prior to surgery. At operation a 3.3X3.2X3.5 cm. parathyroid adenoma weighing 13.8 gm. was removed from the left lower thyroid pole.

Exactly 1 hour prior to the removal of the parathyroid adenoma, 200 µc of Se^{75} selenomethionine was injected intravenously. Serial blood samples were taken throughout surgery and thereafter. Total radioactivity was determined in the parathyroid adenoma and blood as well as in samples of surrounding normal muscle and thyroid removed at operation. In addition, the tissues were homogenized and treated with cold 5 per cent trichloroacetic acid to separate the protein (TCA precipitable) and nonprotein (TCA soluble) radioactivity. The blood samples were similarly treated.

Figure 2 shows the distribution of radioactivity in parathyroid, muscle and blood. It is evident that per gram of tissue the greatest total radioactivity 1 hour after the administration of the radioactive amino

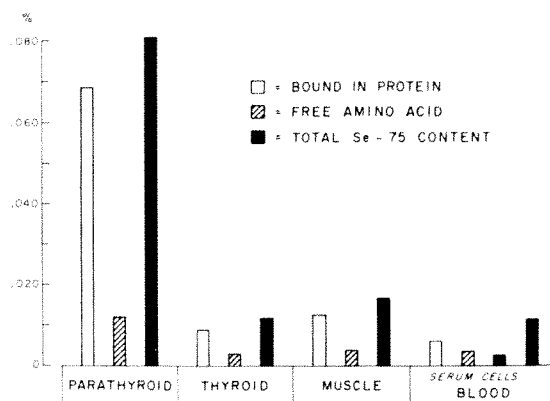


FIG. 2. Distribution of radioactivity in human parathyroid, thyroid, muscle and blood 1 hour following the injection of 200 µc of Se^{75} selenomethionine. Ordinate values in per cent of injected dose per gram of tissue or milliliter of blood.

acid is to be found in the parathyroid. The relative radioactivity of these tissues was: parathyroid to thyroid 7.8:1, parathyroid to strap muscle 5.7:1 and parathyroid to blood 8.6:1. It is also evident from Figure 2 that over 90 per cent of the radioactivity is found in protein at 1 hour, which implies that considerable synthesis of parathyroid hormone had taken place during this period.

The relative parathyroid to thyroid radioactivity was studied in 2 other patients 24 hours following the administration of Se^{75} selenomethionine. The first patient received cytomele preoperatively; a parathyroid adenoma was removed at surgery. The ratio of parathyroid to thyroid radioactivity per gram of dried weight was found to be 18.6:1. The second patient did not receive any thyroid derivatives preoperatively and was found to have parathyroid hyperplasia on exploration. The relative parathyroid to thyroid radioactivity was 2.5:1. This decreased ratio was due to an absolute increase in thyroid radioactivity and suggests that thyroxine does suppress the uptake of selenomethionine in the normal human thyroid and, further, that this suppression is requisite to obtaining a high relative concentration of the amino acid in parathyroid tissue.

The time course of serum radioactivity was studied extensively in another patient (Fig. 3). Following intravenous injection, the serum radioactivity falls abruptly as the amino acid is distributed into various tissues. The minimum is reached at 30 minutes. The serum activity then rises again, the radioactivity now being trichloroacetic-precipitable and presumably associated with newly synthesized, circulating serum proteins.

Similar curves have been obtained with 6 other patients. The minimum serum radioactivity has been found to occur at from 20 to 40 minutes after injection. One might, therefore, expect to encounter minimal interference by circulating radioactivity when photoscans are carried out during this interval.

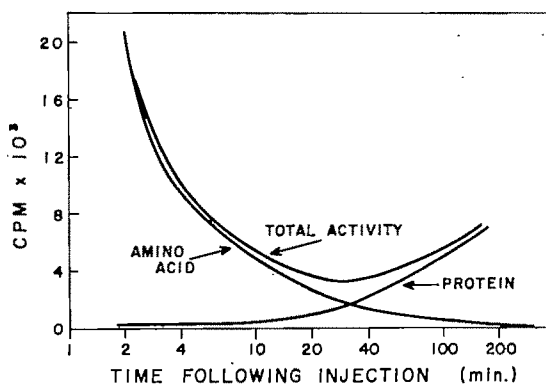


FIG. 3. Time course of serum radioactivity following the intravenous injection of Se^{75} selenomethionine. The radioactivity has been fractionated into trichloroacetic acid soluble (amino acid) and trichloroacetic acid precipitable (protein) components.

CLINICAL APPLICATIONS

Since the selective uptake of selenomethionine could be demonstrated by the human hyperactive parathyroid in the first hour following administration of the labeled amino acid, this information was applied to external scanning in 7 of our own patients (summarized below) and 3 referred from outside hospitals.

CASE STUDIES

MC (PBBH No. 4-78-62) was a 45 year old woman with a history of recurrent hypercalcemia, repeated nephrolithiasis and duodenal ulcer. Her serum calcium was 5.3 to 5.6 mEq./L., phosphorus 0.8 to 1.1 mM., blood urea nitrogen 74 mg. per cent. Tubular reabsorption of phosphate was 78 per cent of normal and her daily urinary calcium excretion on a 200 mg. calcium diet was 141 to 321 mg.

WC (PBBH No. 4-75-52) was a 20 year old man with a history of nephritis. He had painful masses over both elbows and hands, and bone roentgenograms were characteristic of hyperparathyroid overactivity. His calcium was 4.2 to 4.3 mEq./L., phosphorus 4.0 to 4.3 mM., alkaline phosphatase 4.5 Bessy Lowry units and blood urea nitrogen 62 to 120 mg. per cent.

DS (PBBH No. 2-91-65) was a 51 year old man admitted for "metabolic bone changes." Calcium was 5.4 to 6.6 mEq./L., phosphorus 0.9 to 1.7 mM., alkaline phosphatase 5.5 Bessy

Lowry units, and blood urea nitrogen 40 to 50 mg. per cent.

PD (PBBH No. 1-00-24). This 44 year old man was admitted for fluoride treatment of osteoporosis. He had a 5 year history of hypercalcemia. Calcium was 4.5 to 5.0 mEq./L., phosphorus 0.9 to 1.0 mM., alkaline phosphatase 1.1 Bessy Lowry units and blood urea nitrogen 19 mg. per cent.

RC (PBBH No. 1-40-61), a 56 year old woman, was admitted for evaluation of anemia, aches and pains, and easy fatigability. A nodule was palpated in the midportion of the right thyroid. Her calcium was 5.9 mEq./L., phosphorus 0.8 mM., alkaline phosphatase 1.9 to 4.2 Bessy Lowry units and blood urea nitrogen 12 mg. per cent. Iodine 131 scan demonstrated an increased concentration of the isotope in an area of the right thyroid lobe. At surgery a thyroid adenoma was found in this location, in addition to a carcinoma of the left lower parathyroid gland.

ML (PBBH No. 4-41-09), a 15 year old girl, had nephrosis at the age of 2. Six months prior to admission she developed uremia and acidosis. On physical examination she had a palpable nodule at the left lower pole of the thyroid. Calcium was 5.6 mEq./L., phosphorus 2.4 to 3.2 mM., alkaline phosphatase 2.8 to 3.6 Bessy Lowry units and blood urea nitrogen 125 mg. per cent.

CM (PBBH No. 0-56-40) was a 51 year old woman with rheumatic heart disease. She was admitted to the hospital for hematuria and kidney stones. On physical examination she had murmurs consistent with mitral stenosis and insufficiency and a nodule was palpated in the region of the right lobe of the thyroid. Her calcium was 5.3 to 6.7 mEq./L., phosphorus 0.9 to 1.3 mM., alkaline phosphatase 3.2 Bessy Lowry units, and blood urea nitrogen 16 mg. per cent. Iodine 131 scanning of her thyroid showed an area of inactivity in the inferior, medial aspect of the right lower pole. She had a thyroid carcinoma at this locus, as well as a hyperplastic parathyroid gland.

All the patients but CM (0-56-40) received 50 μ g. of cytomel twice daily for 3 to 8 days prior to the administration of selenomethionine. An intravenous injection of 200 μ c of ^{75}Se selenomethionine was then made and scanning was begun, usually within 5 minutes after the administra-

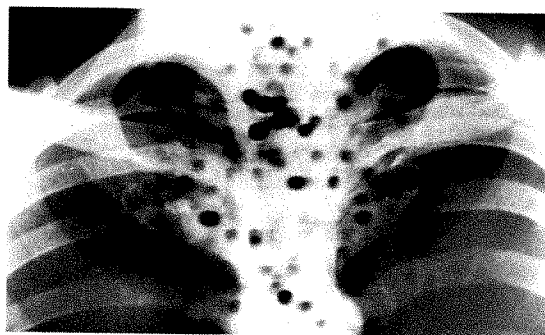


FIG. 4. ^{75}Se selenomethionine photoscan of patient DS (2-91-65). The area of increased density, indicated by the arrow, was subsequently found to be the location of a hyperplastic parathyroid gland at the thoracic inlet.

tion of the isotope. Several consecutive scans were run on each patient over a 4 hour period and the interpretations made on the basis of persistent foci of increased activity as judged by superimpositions of the individual transparencies. Topographic

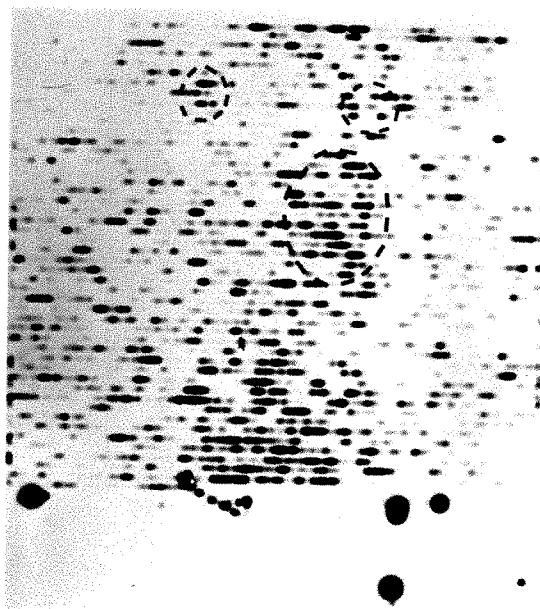


FIG. 5. ^{75}Se selenomethionine photoscan of patient ML (4-41-09). The outlined areas of increased density correspond to the location of hyperplastic parathyroid glands. The largest focus of parathyroid activity was over the clinically palpable nodule. The four large dots are for purposes of topographic orientation. The unmarked area of increased activity at the lower, central portion of the scan corresponds to the manubrium sterni.

control is achieved by roentgen-ray orientation or skin marking. A Picker Magnascanner with a 3 inch crystal was used for these initial studies.

Figure 4 is the scintillation scan obtained in patient DS. The area corresponding to an increased concentration of radioactivity was subsequently established as the site of a parathyroid adenoma. Figure 5, a photoscan of patient ML, shows 1 large and 2 small foci of increased radioactivity. At surgery, 3 hyperplastic glands were located in corresponding areas. The average diameter of the largest gland (left lower) was 3 times that of the other 2.

Table 1 is a summary of the results obtained with the 10 patients. The number of days of cytomel administration and the

interpretation of the scans, as well as the surgical and pathologic findings are given.

In Patients 1 through 6 there was good agreement between the interpretation of the scans and the surgical findings. Four cases of chief cell hyperplasia, 1 case of parathyroid adenoma and 1 case of parathyroid carcinoma comprised this group. In Patient 4, only one area of increased radioactivity was seen on the scan, while 2 hyperplastic glands were found, the greater degree of hyperplasia being in the gland with topographic correspondence to the site of increased radioactivity.

Patient 1, who had a past history of recurrent hypercalcemia and hypercalcuria, was found, while in the hospital, to have a high normal serum calcium and low normal

TABLE I

RESULTS OF SELENOMETHIONINE SCANNING IN 10 PATIENTS WITH PROVEN PARATHYROID PATHOLOGY

Patient (days of cytomel administration)	Scan Report	Surgical Findings	Pathology
1. MC 4-78-62 (5 days)	Increased radioactivity, right lower pole of thyroid	Parathyroid nodule at right lower pole of thyroid	Parathyroid adenoma
2. WC 4-75-52 (3 days)	Increased radioactivity at each thyroid pole	Four hyperplastic parathyroid glands, one at each thyroid pole	Chief cell hyperplasia. Secondary hyperparathyroidism
3. DS 2-91-65 (3 days)	Increased radioactivity at thoracic inlet	Parathyroid nodule removed from thoracic inlet	Chief cell hyperplasia
4. PD 1-00-24 (8 days)	Increased radioactivity, right upper lobe of thyroid	Normal sized parathyroid glands found at right upper, right lower and left lower poles of thyroid	Chief cell hyperplasia of both right glands, upper greater than lower. Normal cellularity, left lower gland
5. RC 1-40-61 (5 days)	Increased radioactivity, left lower pole of thyroid	Abnormal parathyroid tissue found in region of left lower pole	Parathyroid carcinoma
6. ML 4-41-09 (4 days)	Large area of radioactivity, left lower pole of thyroid; moderate, symmetric areas of radioactivity, both upper poles	Large hyperplastic parathyroid gland found at left lower thyroid pole, smaller glands found at both upper poles	Chief cell hyperplasia of all 3 parathyroid glands. Secondary hyperparathyroidism
7. CM 0-56-40 (none)	Thyroid gland radioactive throughout. No definite area of relatively increased radioactivity seen	Hyperplastic parathyroid gland at right lower thyroid pole	Chief cell hyperplasia
8. AK USPH Hosp. Brighton, Mass. (4 days)	Low midline area of radioactivity	Left lower pole parathyroid nodule	Parathyroid adenoma
9. MK Mass. Gen. Hosp., Boston, Mass. (4 days)	No definite, localized area of increased radioactivity visualized	Large left upper pole parathyroid nodule	Parathyroid adenoma
10. NR Beth Israel Hosp., Boston, Mass. (4 days)	No definite, localized area of increased radioactivity visualized	Right lower pole parathyroid nodule	Parathyroid adenoma

serum phosphorus. A bone biopsy of the iliac crest was reported as normal. Selenomethionine scanning showed an area of increased radioactivity in the right lower pole of the thyroid and at surgery a parathyroid adenoma was found at this site. This patient's laboratory findings suggest that her parathyroid disease was in a state of relative quiescence, yet sufficient isotopic uptake obtained to produce a positive photoscan.

Patient 7 received no cytomel and selenomethionine scanning outlined the entire thyroid gland. The patient also received iodine 131 prior to the selenomethionine scan, which raised the possibility that the radioactivity visualized might have been from this source despite efforts to eliminate it by spectrometric adjustments of the receiver. On the other hand, Patient 5 also received I^{131} 25 days prior to Se^{75} selenomethionine. A photoscan taken with the I^{131} window at the time of selenomethionine administration showed increased radioactivity in the right thyroid, from which a thyroid adenoma was subsequently removed. Scanning performed with the Se^{75} window failed to demonstrate any increased radioactivity in the right thyroid, while increased radioactivity was demonstrated on the left at the locus of a parathyroid carcinoma. These observations support the thesis that the visualized thyroid outline on photoscanning the cervical region of Patient 7 with the selenium window was due to selenomethionine uptake by the unsuppressed thyroid.

In Patient 8, a parathyroid adenoma was found at surgery but its location did not correspond exactly to the position of increased radioactivity seen in the photoscan. In Patients 9 and 10, no foci of undoubted radioactivity were found in correspondence to the location of parathyroid adenomas found at surgery. These last 2 patients must be classified as false negative results.

CONCLUSIONS

The utilization of Se^{75} selenomethionine for external scanning shows promise for the preoperative localization of abnormal para-

thyroid tissue. Rodent experiments demonstrate that radioactive, tritiated methionine is concentrated in the hyperactive parathyroid to a greater extent than it is in surrounding muscle and thyroxine-suppressed thyroid tissue. The distribution of radioactive selenomethionine in human parathyroid, thyroid and cervical musculature follows the same patterns as its tritiated sulfur counterpart does in the animal.

Out of a group of 10 patients who had cervico-mediastinal scans following the administration of selenomethionine, the procedure was helpful in localizing abnormal parathyroid tissue in 6. In 1 patient (AK) the region of radioactivity did not correspond precisely to the location of a surgically found parathyroid adenoma, and in 2 patients (MK, NR) with adenomas no definite area of increased radioactivity was visible on the scan. The visualization of the entire thyroid in 1 patient (CM) who failed to take cytomel prior to selenomethionine administration precluded any possibility of localizing a hyperplastic parathyroid.

It is to be expected that technical advances in scintillation scanning will improve the accuracy and precision of the method proposed for the clinical evaluation of parathyroid pathophysiology.

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The Se^{75} selenomethionine was supplied by E. R. Squibb & Sons. A Picker Magnascanner was used for the photoscans.

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DISSOCIATION OF I^{131} FROM RADIOPHARMACEUTICALS AS MEASURED BY THYROID UPTAKE*

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AS THE utilization of the I^{131} labeled radiopharmaceutical preparations increases, the stability of the compounds used becomes of increasing importance for assessing the results of a given test and for determination of the radiation dose to the patient. This is of particular interest to the workers in nuclear medicine and other related fields.

PROCEDURE

The measurement of thyroid uptake of I^{131} is an adequate and readily available procedure for evaluating dissociation of I^{131} from the original labeled preparation, and was employed in this experiment.

The patient was given a tracer dose of I^{131} labeled preparations for the specific study, and was returned in 24 hours for the thyroid uptake determination. The Picker Magnascanner, calibrated by using a wide angle collimator and a discriminator setting of 300–425 kev., was used to measure the thyroïdal uptake. A standard tracer from the same lot from which the patient received his dose was put into a special container and placed 25 cm. from the end of the collimator (50 cm. from the crystal). This standard was counted for 1 minute, and corrected for room background. The patient was placed under the machine with his neck hyperextended and the activity of the thyroid gland was counted with the same collimator at the same distance as the phantom was counted. A spot on the patient's thigh, about as large in diameter as the patient's neck, was chosen and counted. The count rate of the thigh was subtracted from the count rate of the thyroid gland to obtain the net thyroid

gland count. The mathematical expression for the 24 hour uptake is

$$\frac{100 \text{ net c/m thyroid gland}}{\text{c/m phantom}}.$$

RESULTS

1. *RISA (Radioactive Iodinated Serum Albumin)*. Following an intravenous tracer dose of RISA of 5 μC (for blood volume determination) to 500 μC (for brain scanning or vascular studies), the 24 hour glandular thyroid uptakes of I^{131} were found to be in the range of 5.8–9.0 per cent (Fig. 1). The average thyroid uptake for 15 patients was 6.8 per cent.

2. *I^{131} Rose Bengal*. Following an intravenous tracer dose of I^{131} rose bengal of 100–200 μC for liver scanning, the 24 hour thyroid uptakes of I^{131} were in the range of 0.0–7.9 per cent (Fig. 1). The average thyroid uptake for 15 patients was 0.9 per cent.

3. *I^{131} Hippuran*. Following an intravenous tracer dose of I^{131} hippuran of 5 μC (for a renogram) to 200 μC (for renal scanning), the 24 hour thyroid uptakes of I^{131} were in the range of 0.0–2.6 per cent (Fig. 1). The average for 15 patients was 0.6 per cent.

4. *I^{131} Triolein*. Following an oral tracer dose of I^{131} triolein of 25–100 μC , the 24 hour thyroid uptakes of I^{131} were found to show a linear relation with the amount of Lugol's solution administered (Fig. 2). Without the administration of the Lugol solution, the thyroid uptakes were in the range of 9.2–18.9 per cent; with 2, 3, and 4 doses of 5 drops each in 1 day, the range of uptakes was 2.1–6.8 per cent, 0.2–2.9 per

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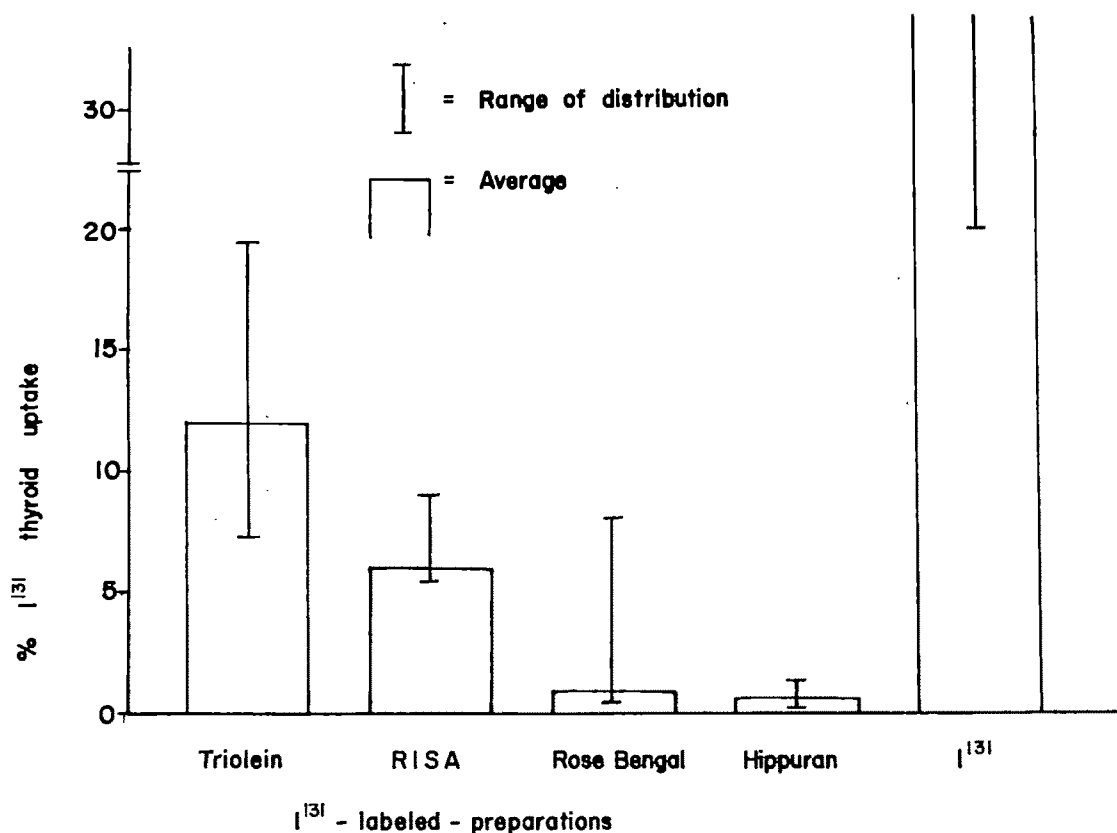


FIG. 1. Range of distribution of I^{131} thyroid uptake from I^{131} labeled radiopharmaceuticals.

cent, and 0.2–1.0 per cent, respectively (Fig. 2).

DISCUSSION

From the given results, the dissociation of I^{131} in the cases of I^{131} rose bengal and I^{131} hippuran by intravenous administration is not significant. This kind of isotopic preparation is most desirable for daily practice since it causes no special concern in preparing the patient for other types of radioisotope studies and, since it is stable, contributes very minimally to the total radiation dose.

RISA by intravenous administration has shown a much higher 24 hour thyroid uptake. Therefore, recommended doses of Lugol's solution should be given to the patient who would be subjected for a study using more than 20 μ c of RISA.

I^{131} triolein by oral administration showed the highest thyroid uptake and the highest

rate of dissociation of I^{131} . This is mostly due to the digestive breakdown in the gastrointestinal system. In preparing the patient for I^{131} triolein absorption study, 4 doses of Lugol's solution, 5 drops each in one day are found to be satisfactory for proper blockage of thyroid uptake of dissociated I^{131} . In the literature, various amounts of Lugol's solution from none to 48 drops in periods from 1 to 3 days are reported.^{1,2,3} The degree of dissociation of I^{131} which was observed in this experiment is presumably a reflection of both inherent and metabolic stability of the 4 compounds.

SUMMARY

1. The stability of various I^{131} labeled compounds, which are currently employed in medicine, was evaluated by I^{131} thyroid uptake studies.

2. I^{131} rose bengal and I^{131} hippuran

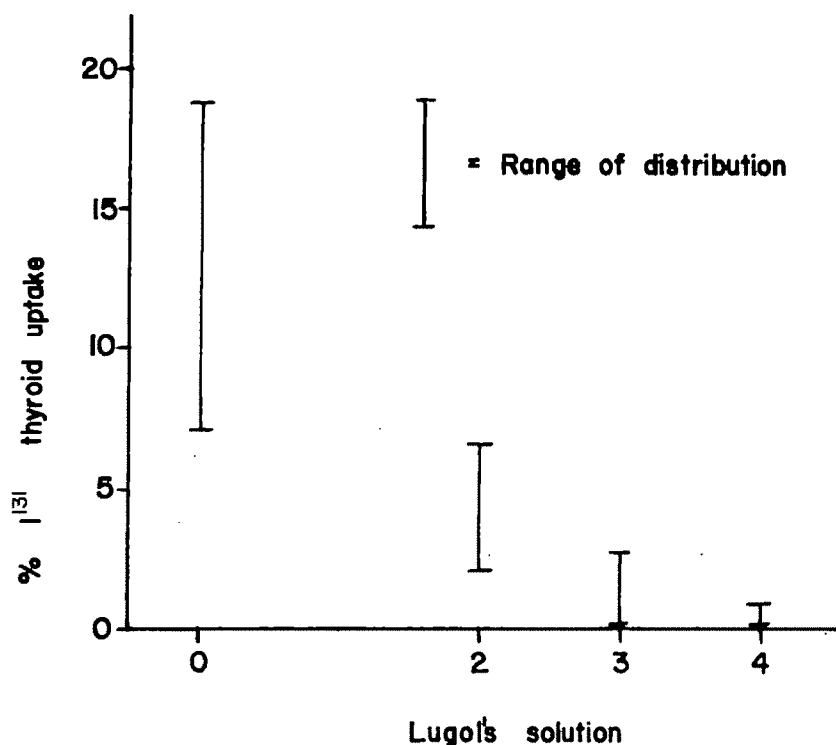


FIG. 2. Degree of 24 hour I^{131} thyroid uptake from oral I^{131} triolein corresponding to doses of Lugol's solution administered.

showed the least I^{131} thyroid uptake and are proven to be the most stable compounds. They are ideal for clinical use.

3. Four doses of Lugol's solution, 5 drops each, in one day are found to be satisfactory for the blockage of the thyroid in preparing the patient for a larger tracer dose of RISA and for an I^{131} triolein study.

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A DIFFERENT APPROACH TO CHEST ROENTGENOGRAPHY: TRIAD TECHNIQUE (HIGH KILOVOLTAGE, GRID, WEDGE FILTER)

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WITH increasing technical development, roentgenography of the chest has steadily improved. The conventional chest roentgenogram, however, still has shortcomings inherent in the present techniques; nearly half of the lung field is seen through superimposed shadows of clavicles, ribs, breast tissue and the heart, which obscure much of the finer detail. When an attempt is made to take a roentgenogram of a patient whose chest measures 26 cm. or more in the posteroanterior projection, the problems become even greater. It is very difficult to obtain a roentgenogram of the same quality of a chest measuring 28 cm. or more that one would expect to achieve in the average patient of lesser measurement.

The main problems which confront us with chest roentgenography can be divided into three categories: (1) lack of penetra-

tion, (2) lack of fine detail, and (3) uneven density.

LACK OF PENETRATION

Figure 1 *A* is a posteroanterior conventional chest roentgenogram of a patient whose chest measures 28 cm. in the posteroanterior projection. There is poor penetration of both bases due to heavy breast tissue. By increasing the kilovoltage from the conventional range of 70-80 kv. to 134 kv., the breast and overlying bone structures are more adequately penetrated (Fig. 1*B*). The increased latitude gained by this elevation in kilovoltage enabled us to better differentiate tissues which are closely similar in density. Thus, the first step toward increasing detail was accomplished. It must be noted, however, that this increase in kilovoltage has resulted in an over-all grayness and haziness

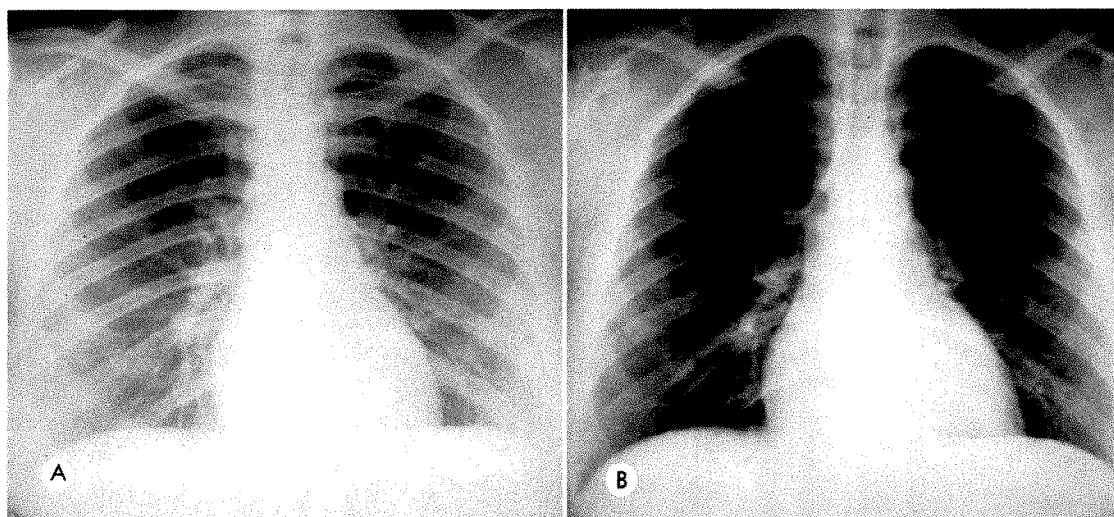


FIG. 1. (*A*) Conventional chest roentgenogram of a woman with adipose breasts. (*B*) With an increase in kilovoltage, the breasts and overlying bone structures are adequately penetrated but the apical regions are overpenetrated.

of detail, which we believe is due to secondary radiation effect. Also, the apical regions are overpenetrated which is undesirable (Fig. 1*B*).

LACK OF FINE DETAIL

To further improve the detail and to overcome the secondary radiation effect, as a second step, we have employed a 12:1, 80 line, stationary grid. This grid is mounted on the front of the chest board and is permanently fastened in its position. The purpose of the grid is the same as that which justifies the use of the Bucky diaphragm; namely, to eliminate scattered radiation and to enhance contrast. Where a 72 inch reciprocating upright Bucky diaphragm is available, this is used in place of the stationary grid. The conventional chest roentgenogram usually demonstrates only the larger pulmonary vessels. By the use of the grid and also by employing a shorter exposure time, we have been able to consistently demonstrate vessels as small as 1 mm. in caliber in the far periphery of the lungs. Several factors made this possible: (a) the latitude allowed by high kilovoltage in differentiating tissues of almost similar density; (b) the penetration of the overlying ribs (now somewhat less obvious because of the penetrating high

kilovoltage); and (c) the shorter exposure time which stops the motion of these smaller pulmonary vessels, making them visible in the periphery of the lung. Figure 2, *A* and *B* demonstrates this in some detail in the posteroanterior view. Figure 3, *A* and *B* demonstrates this again in the lateral view.

When we first used this technique, we over-read each roentgenogram, for we were seeing small peripheral vessels in the bases and beneath the ribs which were not previously visible. Even now, we must interpret a chest roentgenogram with a different approach than the one that we had been accustomed to when using the conventional technique. At the outset over-reading produced a diagnosis of "pulmonary congestion," "pulmonary fibrosis," etc., in many normal patients. Follow-up studies at our request taught us that these newly visible markings were small normal vessels which we had not previously been able to visualize. We, therefore, as a third step, had to develop a new standard for normality.

UNEVEN DENSITY

This step consisted in correcting the unevenness in density between the apices and the bases. As one views the pyramid shape of the chest from the side (Fig. 4), it be-

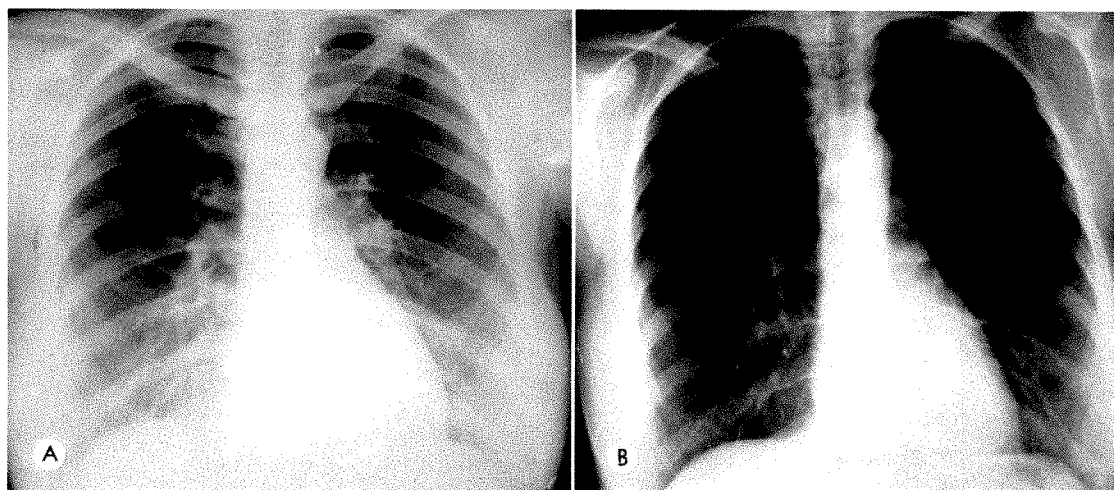


FIG. 2. (*A*) Conventional posteroanterior chest roentgenogram. (*B*) High kilovoltage chest roentgenogram using a grid but not the wedge filter, still showing that the apices are overpenetrated.

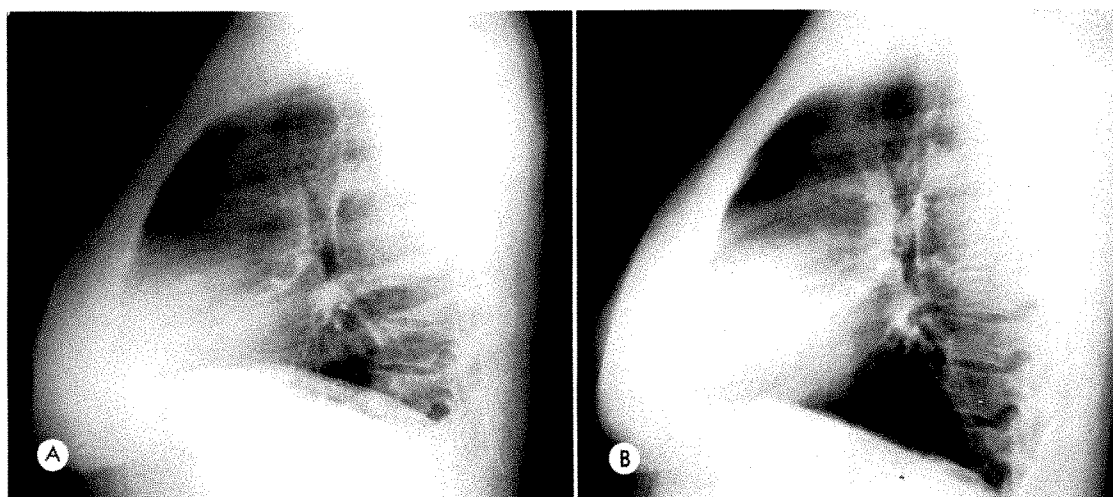


FIG. 3. Same patient as in Figure 2. (A) Conventional lateral chest roentgenogram. (B) High kilovoltage lateral chest roentgenogram, using a grid but not the wedge filter, also shows the overpenetrated apices.

comes quite obvious that less radiation is needed for a satisfactory roentgenogram of the narrow apical portion than for the wider basilar portion. This is especially true in the case of the larger women with heavy breast tissue (Fig. 5A). Therefore, we have utilized a reversible wedge filter cone. In the posteroanterior projection by increasing the kilovoltage, we have penetrated the heavy breast tissue but have overexposed and blacked out the apices (Fig. 5B). With the use of the reversible wedge filter cone, we have decreased apical exposure and obtained the result seen in Figure 5C. Even in an average patient the

excellent detail produced by this triad technique (high kilovoltage, grid, and wedge filter) is quite apparent when compared to the conventional chest roentgenogram (Fig. 6, A and B).

LATERAL CHEST ROENTGENOGRAPHY

The greatest advantage of this triad technique, however, has been observed in lateral chest roentgenography. Here, the same wedge filter cone is used in reverse. Its principle is shown diagrammatically in Figure 7. While the lung is still pyramid shaped, the soft tissues of the trunk at chest level form an inverse pyramid. Several factors enter into the problem of uneven density in the lateral view. Heavy muscles absorb considerable radiation, resulting in underexposed or light apices. In direct contrast, the triangular area of almost pure air-containing lung, which is always found behind the heart, absorbs very little radiation, resulting in an overexposed or blacked out area at the base. Thus, by placing the thicker part of the filter over the base to cut down radiation and the thinner part over the apex to allow more radiation, a lateral chest roentgenogram of excellent quality is produced (Fig. 8, A and B). The wedge filter cone is made of aluminum and the wedge filter on the cone is

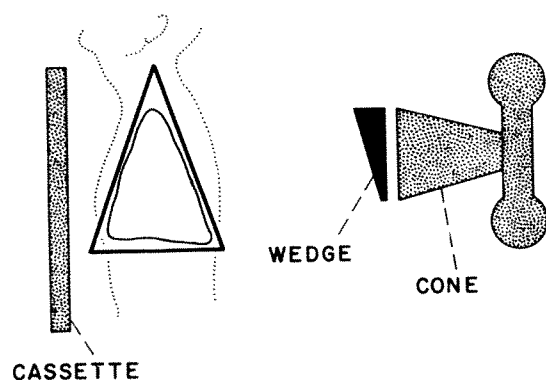


FIG. 4. Diagram showing the anatomic reasons for using wedge filter in the posteroanterior projection.

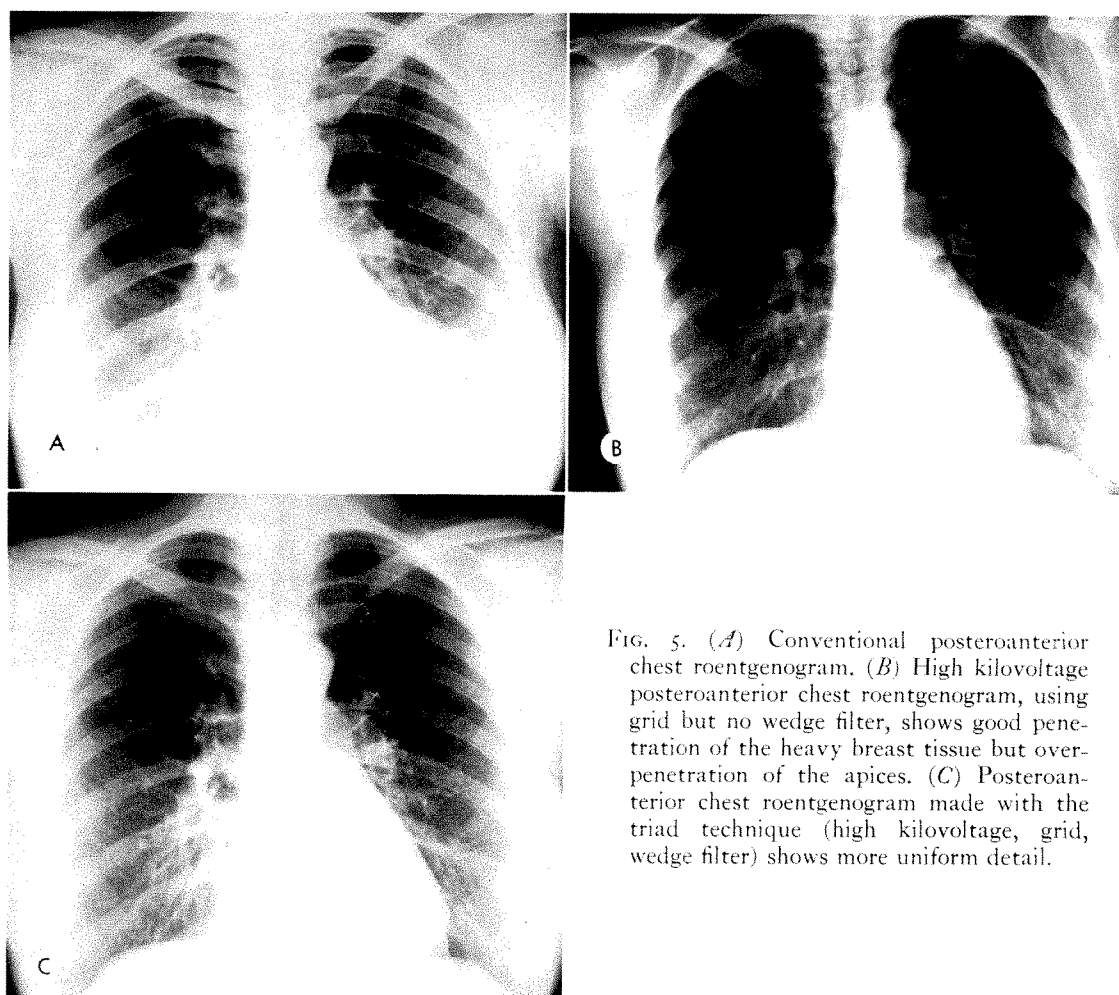


FIG. 5. (A) Conventional posteroanterior chest roentgenogram. (B) High kilovoltage posteroanterior chest roentgenogram, using grid but no wedge filter, shows good penetration of the heavy breast tissue but over-penetration of the apices. (C) Posteroanterior chest roentgenogram made with the triad technique (high kilovoltage, grid, wedge filter) shows more uniform detail.

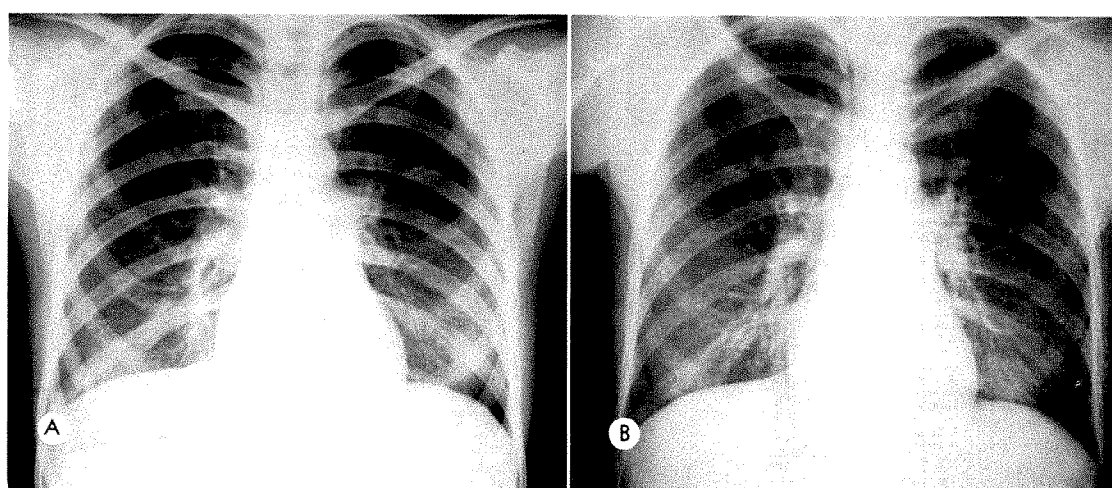


FIG. 6. (A) Conventional posteroanterior chest roentgenograms of an average sized patient. (B) Posteroanterior chest roentgenogram made with the triad technique in the same patient. The greater detail in B is apparent.

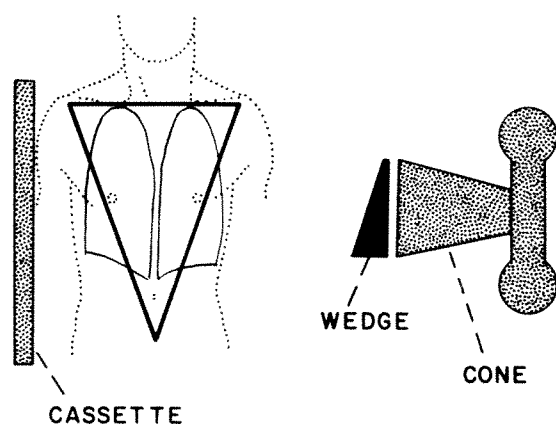


FIG. 7. Diagram showing the anatomic reasons for using wedge filter in the lateral projection.

completely reversible in seconds (Fig. 9). This cone, we have found, can also be used for roentgenography of other anatomic parts with the substitution of desired wedges.

We have been able to demonstrate details in the apices of the lung and the anterior lower mediastinum which were not at any time demonstrated in the conventional lateral chest roentgenograms of the same patient. In Figure 10, *A* and *B*, a conventional lateral chest roentgenogram of a woman, whose chest in the posteroanterior projection measured 38 cm., is com-

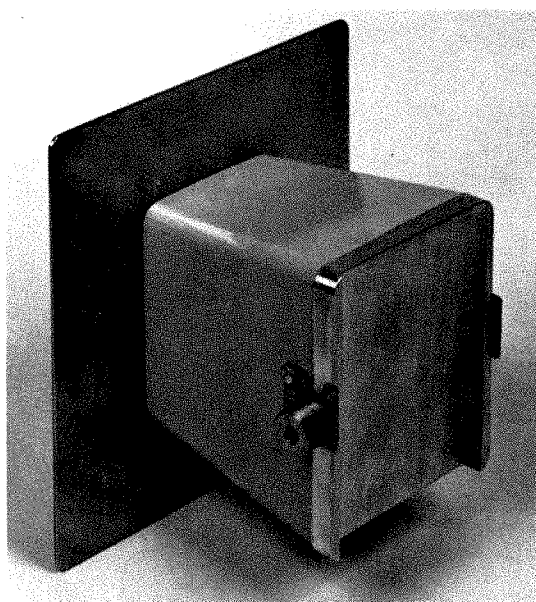


FIG. 9. The reversible wedge filter cone.

pared with a chest roentgenogram of the same woman made by the triad technique. The improvement in detail is quite evident.

EQUIPMENT

For our procedure we have used a 500 ma. machine with 150 kv. Dynamax tube, a Lysholm 80 line grid and Cascade's reversible wedge filter cone. This study com-

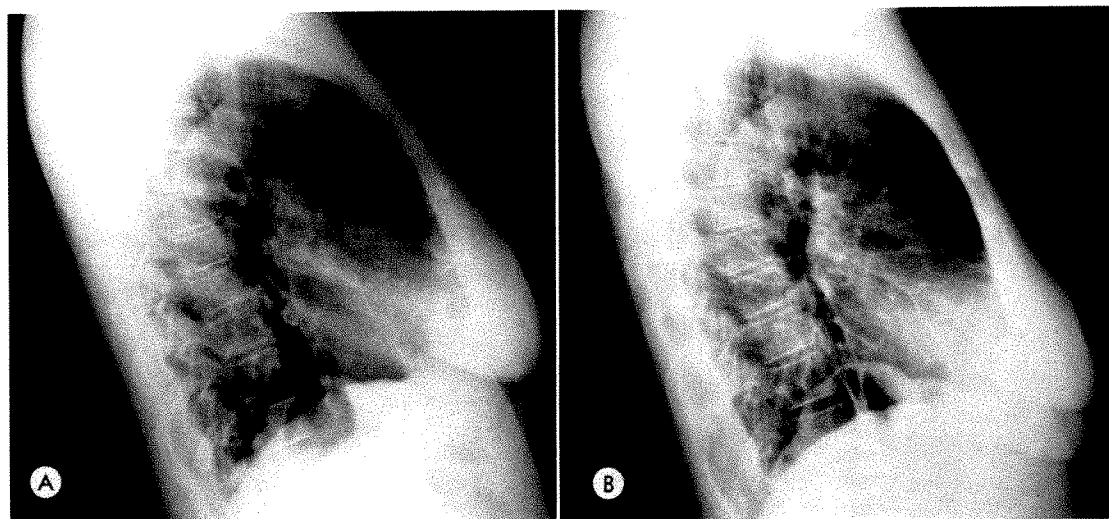


FIG. 8. (*A*) Conventional lateral chest roentgenogram. (*B*) Lateral chest roentgenogram made with the triad technique.

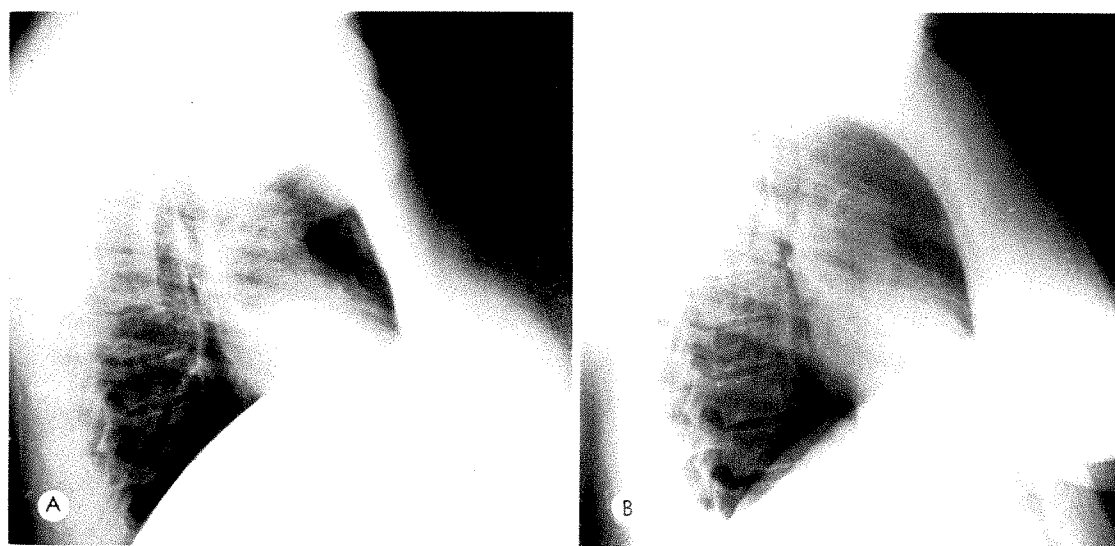


FIG. 10. (A) Conventional lateral chest roentgenogram of a woman whose chest in the posteroanterior projection measured 38 cm. (B) Lateral chest roentgenogram of the same woman, using the triad technique.

prises over 3,000 chest roentgenograms using Eastman Blue Brand film with Du Pont intensifying screens. Tables I and II list the factors of the techniques that have been worked out during the past year to produce some of the roentgenograms in this presentation. We would like to emphasize that the exposure is done with a maximum of 200 to 300 ma., and an optimum kilovoltage of 134 kv. for the posteroanterior and 124 kv. for the lateral view. It is our ex-

perience that a fixed kilovoltage tends to eliminate some of the technicians' errors, especially those in measurement, and that when there is only one variable, namely, the time, errors are reduced to minimum, permitting consistent reproduction of the examination on the same patient.

As further technical advances are made, it is expected that chest roentgenography will continue to improve. The use of the triad technique, especially in lateral chest

TABLE I

POSTEROANTERIOR CHEST TECHNIQUE EMPLOYING GRID AND WEDGE FILTER

19-21 cm.	200 ma.	134 kv.	1/60 sec.	72 inch distance
22-24 cm.	200 ma.	134 kv.	1/40 sec.	72 inch distance
25-27 cm.	200 ma.	134 kv.	1/30 sec.	72 inch distance
28-30 cm.	200 ma.	134 kv.	1/20 sec.	72 inch distance

TABLE II

LATERAL CHEST TECHNIQUE EMPLOYING GRID AND WEDGE FILTER

25-27 cm.	200 ma.	124 kv.	1/20 sec.	72 inch distance
28-30 cm.	200 ma.	124 kv.	1/15 sec.	72 inch distance
31-33 cm.	200 ma.	124 kv.	1/10 sec.	72 inch distance
34-36 cm.	200 ma.	124 kv.	3/20 sec.	72 inch distance
37-39 cm.	200 ma.	124 kv.	2/10 sec.	72 inch distance

roentgenography, seems to represent a worthwhile contribution in this direction.

SUMMARY

1. Series of chest roentgenograms were made of a group of consecutive patients, using the conventional technique and a new triad technique (high kilovoltage, grid, wedge filter) in an effort to solve many of the present problems encountered in conventional chest roentgenography.

2. It was found that the main problems in conventional chest roentgenography could be classified under three headings:

(1) poor penetration, (2) lack of fine detail, and (3) uneven density. These were solved, in part, by the use in sequence of high kilovoltage to solve problem (1), a fixed grid and a very short exposure time to solve problem (2), and a reversible wedge filter cone to solve problem (3).

3. It is concluded from this study that superior chest roentgenograms, especially in the lateral view, can be obtained by the use of the triad technique.

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SERIAL 2 FILM METHOD OF DIFFERENTIATING SLIDING AND PARA-ESOPHAGEAL HERNIAS

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FOR many years I have used a simple objective method of differentiating between sliding and para-esophageal hiatus hernias. The method was devised because it was frequently difficult to determine the type of hernia shown on ordinary roentgenograms and the written note of the fluoroscopic findings often only alluded to the fact that a hiatus hernia was *present*. Furthermore, routine roentgenographic studies often showed the hernia to be filled with air or barium, with or without visualization of the barium-filled esophagus adjacent to the hernia. Such roentgenograms, although of good quality, frequently did not permit the identification of the esophagogastric junction.

The identification of the esophagogastric junction is important because, if it can be identified above the diaphragm, the hernia is obviously of the "sliding" type; *i.e.*, the esophagogastric junction has "slid" above the esophagogastric hiatus of the diaphragm. On the other hand, if the esophagogastric junction is below the diaphragm, the associated hernia cannot be of the sliding type, and must, therefore, be of the para-esophageal type. Thus, the radiologic identification of the location of the esophagogastric junction with relationship to the diaphragm is the one requirement for accurate differential diagnosis of these types of hernia.

METHOD

A simple, precise, and objective method for locating the esophagogastric junction consists of making 2 serial roentgenograms with the patient in the prone position in which the hernia will be shown by "air contrast" technique if it has first been filled with barium with the patient in the supine position. The 2 serial roentgenograms (Fig. 1, *A* and *B*; 2, *A* and *B*; and 3, *A* and *B*)

are made during the routine fluoroscopic examination with the patient holding his breath for the entire procedure. The first roentgenogram is made as the bolus of ingested thick barium cream or paste reaches the level of the proximal portion of the hernia (Fig. 1*A*; 2*A*; and 3*A*). The second study is made 2 to 4 seconds later as the bolus enters (or appears to enter) the hernia (Fig. 1*B*; 2*B*; and 3*B*).

The esophagogastric junction can be identified correctly during fluoroscopy by noticing whether the hernia fills or does not fill with the swallowed barium bolus, but it is much more easily and objectively identified by studying the 2 serial roentgenograms. If a single swallowed barium bolus is seen to enter the air-filled hernia with the patient in the prone-oblique position, the esophagogastric junction must be located *above* the diaphragm; *i.e.*, there is no way for the hernia located above the diaphragm to fill from the esophagus unless the esophagogastric junction is located above the diaphragm. Conversely, if the esophagogastric junction is located *below* the diaphragm, as in the case of para-esophageal hernias, the single barium bolus will only fill and outline the lumen of the esophagus as it passes through the region of the air-filled hernia, which is often superimposed over the esophagus, thereby making it difficult or impossible to identify the esophagogastric junction on a single roentgenogram, particularly if the hernia is full of barium. However, the bolus of barium coursing through the lower esophagus does not enter a para-esophageal hernia, but passes into the infradiaphragmatic portion of the stomach and hence into the gastric antrum, from which location it cannot flow "uphill" to enter the hernia as long as the patient remains in the prone-oblique position.

Although the supradiaphragmatic or

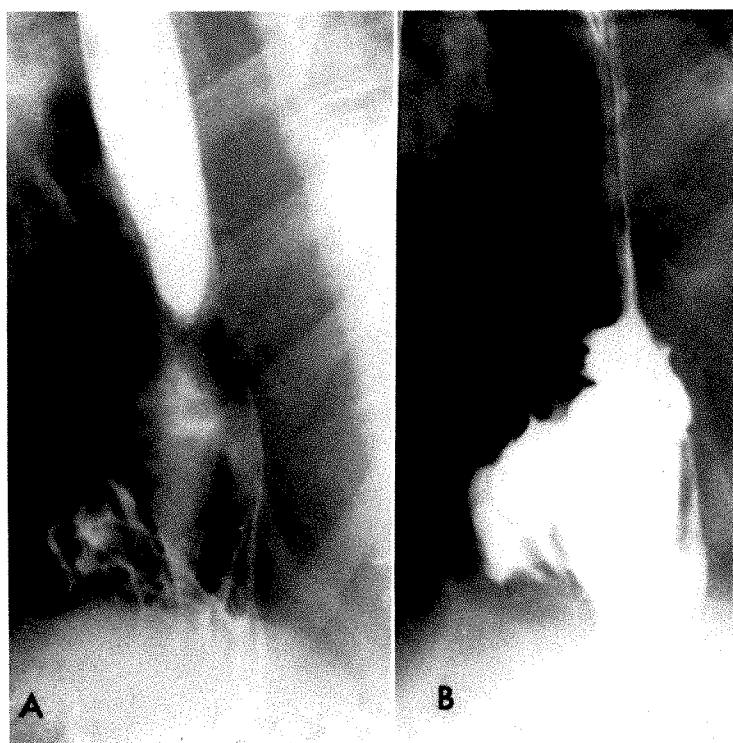


FIG. 1. (A) Roentgenogram shows barium bolus approaching the proximal end of the hernia. (B) Roentgenogram made 2 or 3 seconds later shows the contracted esophagus which has propelled the bolus into a hernia, thus proving that the esophagogastric junction is *above* the diaphragm; *i.e.*, the hernia is of the sliding type.

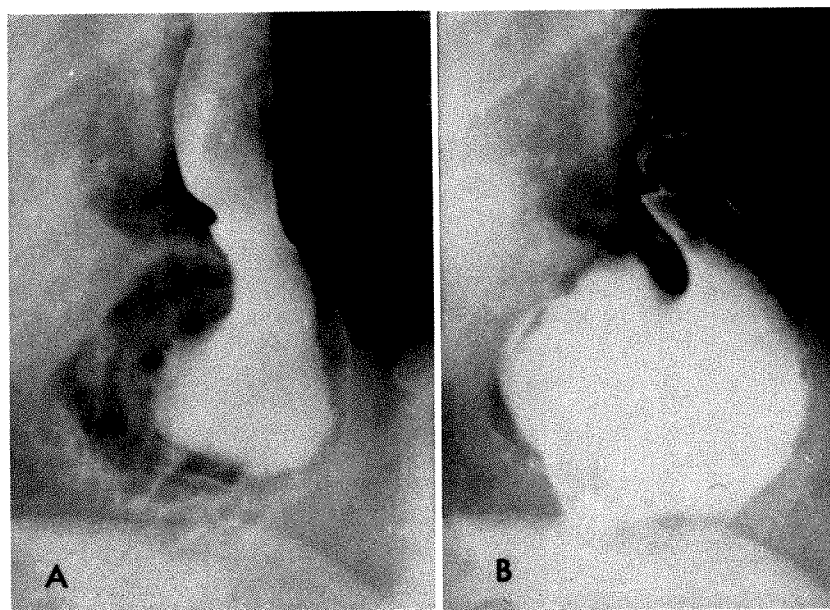


FIG. 2. (A) Roentgenogram shows barium bolus beginning to enter the hernia, whereas B made 2 or 3 seconds later shows the entire bolus obviously within the hernia, thus proving that the esophagogastric junction lies *above* the diaphragm; *i.e.*, the hernia is of the sliding type.

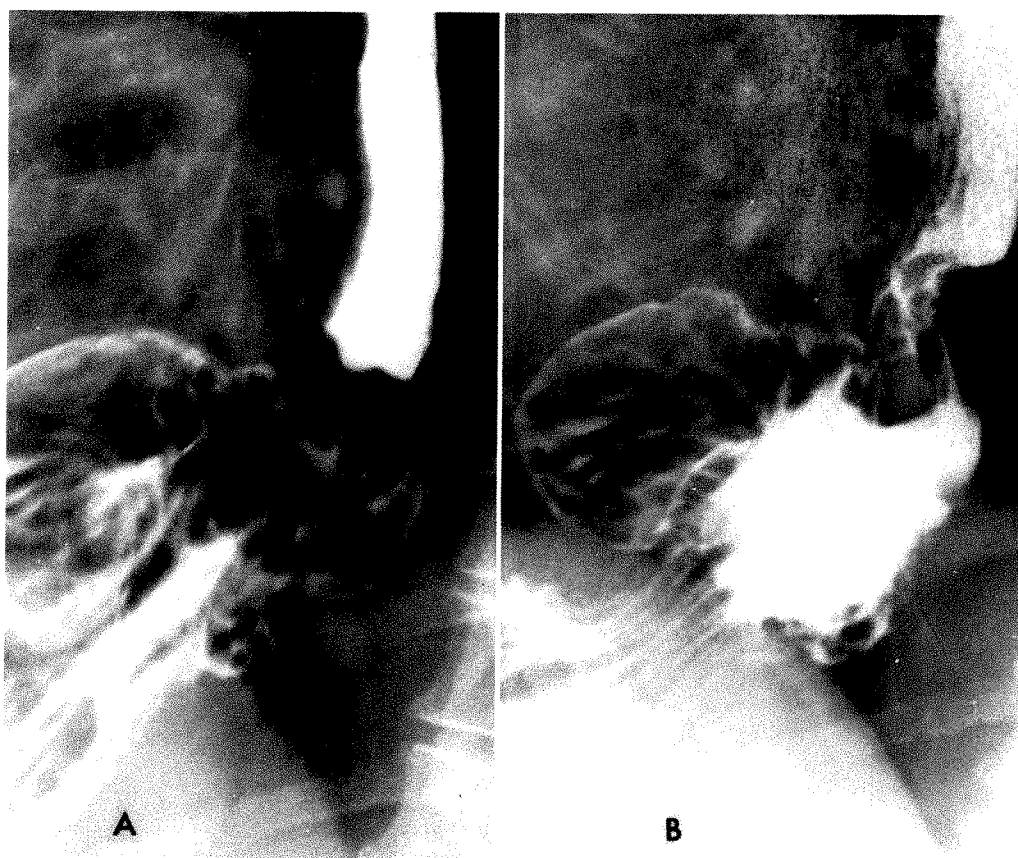


FIG. 3. (A) Roentgenogram shows barium bolus about to enter region of hernia. (B) Roentgenogram made 2 seconds later shows that the barium bolus has obviously entered the hernia and is beginning to spread between the gastric folds. The esophagogastric junction is, therefore, obviously *above* the diaphragm, and the hernia is of the sliding type.

subdiaphragmatic location of the esophagogastric junction can also be established by careful observation of the swallowed barium bolus during fluoroscopy, the 2 serial film method provides objective proof of the diagnosis, in contrast to the lack of objective proof following routine fluoroscopy or the routine postfluoroscopy single film studies. This serial 2 film method is also time-saving and economical, because it precludes the necessity for making roentgenograms in multiple projections of the barium-filled esophagus and hernia, a task frequently left to the technician following fluoroscopy, utilizing methods which leave much to chance, and are not diagnostic in many instances. Cine techniques, although also clearly diagnostic, are not necessary. As a matter of fact, the 2 serial film method

represents a simplified, but adequate, "cine" method of making the diagnosis.

CONCLUSION

An economical simple 2 spot film serial study made under fluoroscopic control with the patient in the prone-oblique position permits clear-cut differentiation between sliding and para-esophageal hiatus hernias. The same principles can also be used to make the fluoroscopic diagnosis, but the serial film method is desirable because it quickly provides objective evidence of the correct diagnosis.

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REMOVAL OF PLUG FROM T-TUBE BY FLUOROSCOPICALLY CONTROLLED CATHETER*

REPORT OF A CASE

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MAINTENANCE of patency of the T-tube inserted into the common bile duct at exploration is of great importance to patient and surgeon. Often, however, clots, grumous material, or even small calculi occlude the T-tube.^{5,8,9} The frequency of obstruction of T-tubes is related to the magnitude of the surgical procedure, the large number of small common and hepatic duct stones, and the length of time that the T-tube is in the common duct. The importance of maintaining free flow through the T-tube is best attested to by the numerous, rather energetic efforts at removal of plugs.^{1,2,4,6,8,10} Many authors have used chemical solvents, such as bile salts,² ethyl ether,⁶ chloroform,⁸ and ethyl alcohol,¹⁰ alone or in conjunction with smooth muscle relaxants.¹ Sterling⁸ stated that he had on occasion removed stones with an infant cystoscope. Because of irritation produced by chemical solvents, their use has been discontinued and, at present, only physiologic saline or water is recommended.⁹ When irrigation is not successful, most surgeons remove the tube and, if necessary, re-explore the common duct.

In the case reported here, a catheter was introduced over a guide wire into the T-tube. It was manipulated under fluoroscopic control, successfully breaking the plug in the proximal limb. The material was aspirated and patency was reconstituted.

REPORT OF A CASE

A 59 year old white salesman was admitted to the Herbert C. Moffitt Hospital with a chief complaint of "stomach trouble." On physical examination a mass was found in the right upper quadrant which was diagnosed as hy-

drops of the gallbladder and possibly carcinoma. At laparotomy, a carcinoma of the gallbladder was found, which extended into the right lobe of the liver. No other evidence of metastatic disease was seen. A cholecystectomy and right hepatic lobectomy were performed. The common duct was explored and T-tube drainage established. Postoperatively, the patient improved until about the seventh day, when biliary flow from the T-tube ceased. A cholangiogram revealed an obstruction of the proximal limb of the T-tube. At this point, T-tube drainage was essential because of the recent closure of the right hepatic duct secondary to the right hepatic lobectomy. The problem was referred to the Department of Radiology where a small polyethylene catheter was inserted through the T-tube over a guide wire. Inspissated bile and blood clots (Fig. 1 through 4) were suctioned out by syringe through the catheter after the guide wire was removed. The procedure was performed under fluoroscopic control using a television monitor in a lighted room. Successful drainage of the T-tube resulted in a decrease in the biliary cutaneous fistula that had developed. Improvement continued and by the twentieth postoperative day the T-tube was removed. The patient was discharged on the thirty-third postoperative day in good condition, with jaundice completely cleared and subsequent spontaneous closure of the biliary cutaneous fistula.

DISCUSSION

In this patient, as in many others, maintenance of free flow of bile through the T-tube was essential for postoperative recovery. In the immediate postoperative interval, re-operation increases morbidity and significantly increases risk of mortality. A biliary cutaneous fistula resulting from the right lobectomy would not have healed if

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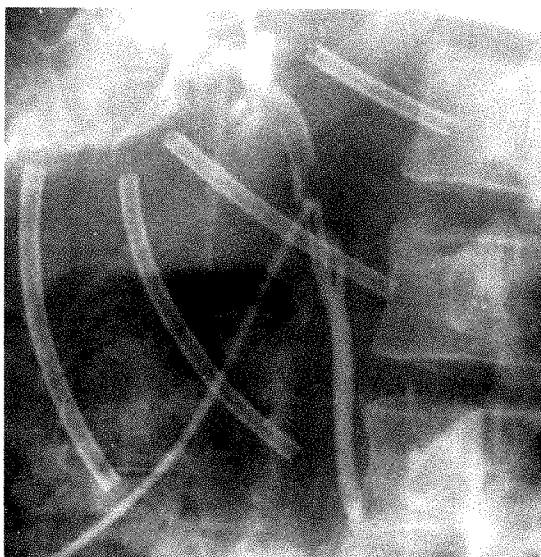


FIG. 1. Cholangiogram shows occlusion of the proximal limb of the T-tube. Contrast material outlines the hepatic duct and the outside of the proximal limb of the tube. The massive biliary cutaneous fistula is demonstrated.

the T-tube in this patient had not remained patent.

The catheter and guide wire were of the conventional type used for percutaneous arterial catheterization in most radiology departments.⁷ As this application gains acceptance, special catheters and instruments undoubtedly will be designed. This would be used under fluoroscopic control for

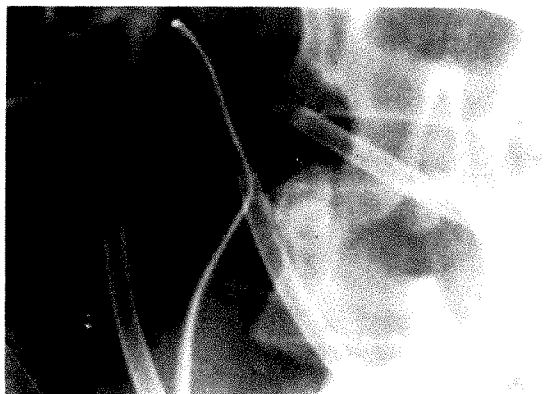


FIG. 2. The metallic guide wire introduced through the T-tube is demonstrated in place. The distal part and tip of the wire are in the proximal limb of the tube.

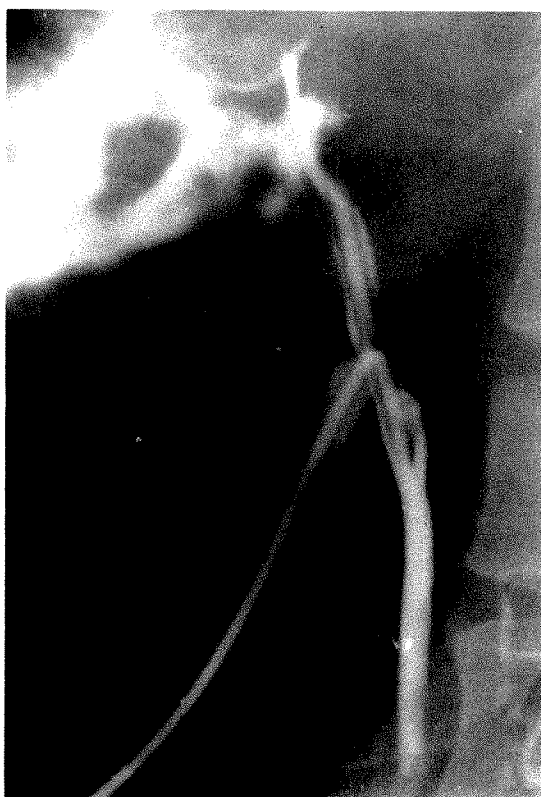


FIG. 3. After the plug of blood clot and inspissated bile were broken by the guide wire and suctioned out through the catheter, the catheter was removed. This cholangiogram shows patency of the entire T-tube and no evidence of any filling defects.

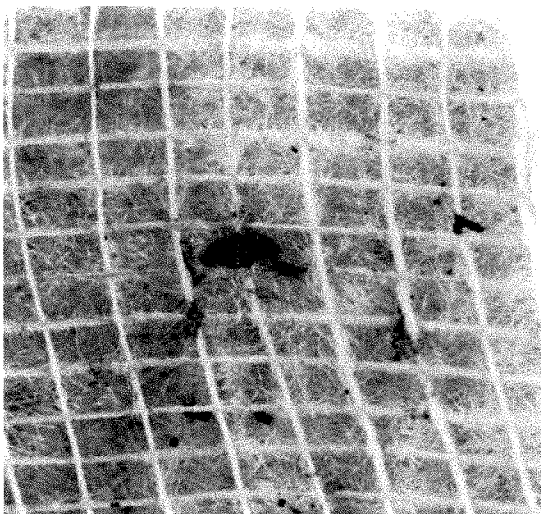


FIG. 4. Blood clots and fragments of inspissated bile that were aspirated from the T-tube. The mesh is that of a gauze sponge.

removal or crushing of calculi in the T-tube or in the bile ducts. Instruments for biopsies of the ductal system, within or outside of the liver, or in the duodenum around the papilla will also undoubtedly follow. Hemostasis could be effected through the catheter and its success judged by introduction of contrast medium and roentgenographic observation. Dotter³ has investigated similar procedures through the vascular approach.

SUMMARY

An occluded T-tube was rendered patent by means of a catheter introduced into the tube over a guide wire, under fluoroscopic control. Blood clots and inspissated bile were broken up by the guide wire and then aspirated through the catheter. The procedure was done in the immediate postoperative period after cholecystectomy and right lobe hepatectomy for carcinoma of the gallbladder. The implications of this approach are discussed.

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A NEW TECHNIQUE FOR SPLENOPORTOGRAPHY*

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ALTHOUGH the problem of splenic circulation, as regards the connection of the arterial capillaries with the splenic sinuses and the relationship of the latter to Billroth's cords has not been satisfactorily solved, there seems to be no doubt about the compartment-like nature of the circulation in the spleen. Da Costa's² work, among others, presents conclusive evidence of this. In fact, if an opaque substance is injected, first through the artery and then through the vein of the same spleen after the arterial and venous hilar branches in the opposite poles have been ligated (Fig. 1), a definite juxtaposition of the two systems will be noted, giving the impression of arteriovenous unity. It, therefore, appears that the splenic circulation is indeed compartmented.

There is no true lobulation by septa, but a certain number of functional units can be observed, corresponding to the orientation of an arterio-venous-axis. After the injection of 12 cc. of lipiodol into a previously ligated hilar branch, the larger vessels become visible in two-thirds of the organ and the injection of an additional 20 cc. produces a clear delimitation of the compartment-like zone corresponding to the ligated branch.

Since the work of Abeatici and Campi,¹ the splenoportographic technique consists of injecting the contrast material into the spleen through a needle with an end opening by a transcutaneous puncture. Variations of this technique, as described by the different authors, have only been in the manner of approaching the spleen, the target always being a thicker area of the spleen, and a constant precaution to avoid spillage of contrast medium into the peritoneal cavity. According to our experience,

this has proved to be only a minor risk, except for the pain common to any of such procedures. The diagram in Figure 2, *A* and *B* shows that, wherever the place of the puncture is, no more than 1 or 2 branches corresponding to the punctured compartment are demonstrated on roentgenograms. The remaining splenic vessels, which converging towards the hilus form the trunk of the splenic vein, are not visualized on these studies.

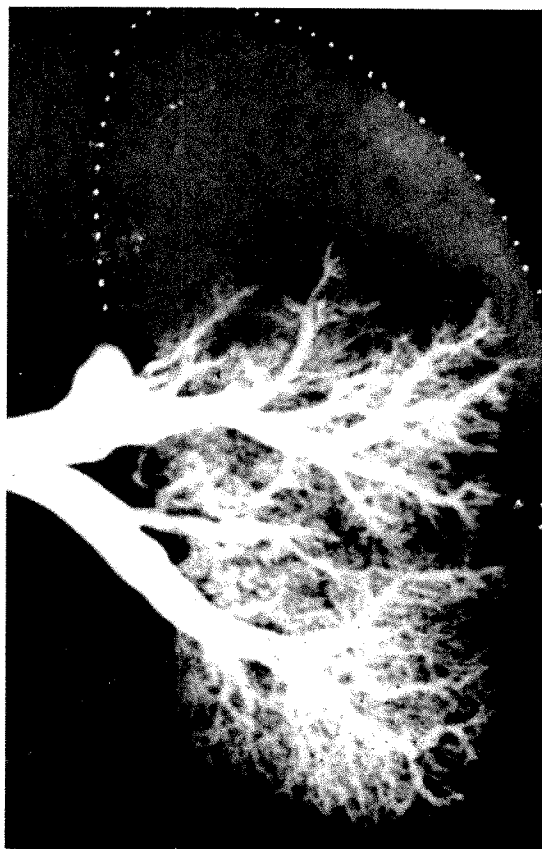


FIG. 1. Contrast material was injected in the splenic vein after tying off a vein of the upper pole. (Reproduced with permission of *Gaz. med. port.*² and J. Celestino da Costa.)

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METHOD

For the demonstration of most of the veins that emerge from the spleen, we devised a needle sealed at the end and provided along one side with several orifices at equal distances (Fig. 3). With this needle we puncture the spleen through its longer axis. At the proximal end of the needle, a mark indicates the side on which the orifices are located and which must be turned towards the splenic hilus. Because of its size and shape, the dog's spleen is ideal for experimenting with the above described needle.

RESULTS

After the animal had been anesthetized, the abdominal cavity was opened and splenoportography was first performed under visual control with 10 cc. of urografin

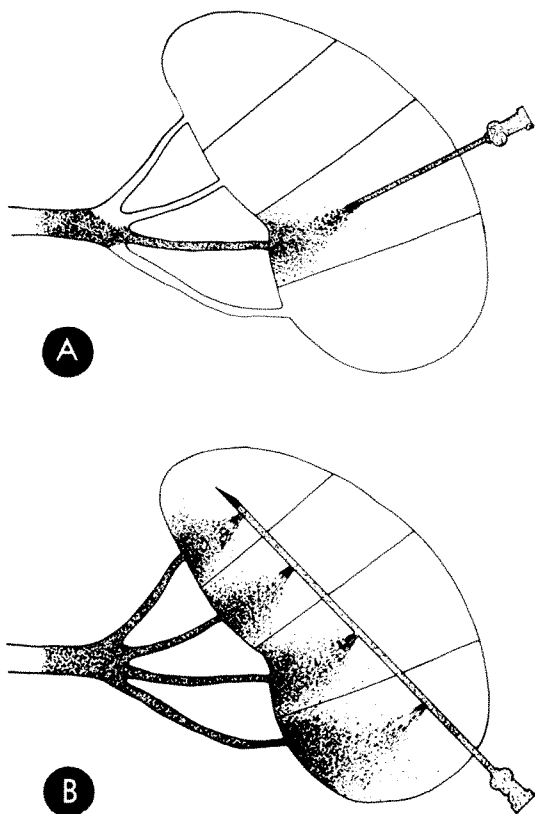


FIG. 2. (A) Injection into the spleen by the conventional method of splenoportography. (B) Injection with the multi-hole needle.

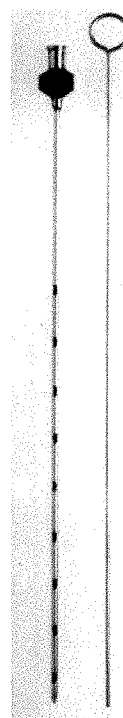


FIG. 3. Multi-hole needle (15 cm.—18/10 mm.).

76 per cent, using a conventional needle with a single end opening. The lower pole of the spleen was punctured. Visualization of a small number of confluent veins leading to the splenoportal trunk was obtained (Fig. 4A).

In the same dog, by employing the multiple side-orifice needle, introduced axially and containing the same amount of contrast material, an important upper polar branch running conflently towards the great splenic drainage trunk was demonstrated (Fig. 4B; and 6).

Following large-scale experimentation in animals, the same multiple side-orifice needle was used in humans.

In the first attempt, to ensure greater safety when introducing the needle along the splenic axis and to prevent any of the terminal orifices from remaining outside of the organ, the splenoportography was performed surgically. Puncture was made with a conventional needle and then with the multiple side-orifice needle, and only 20 cc. of contrast medium was injected in both instances.

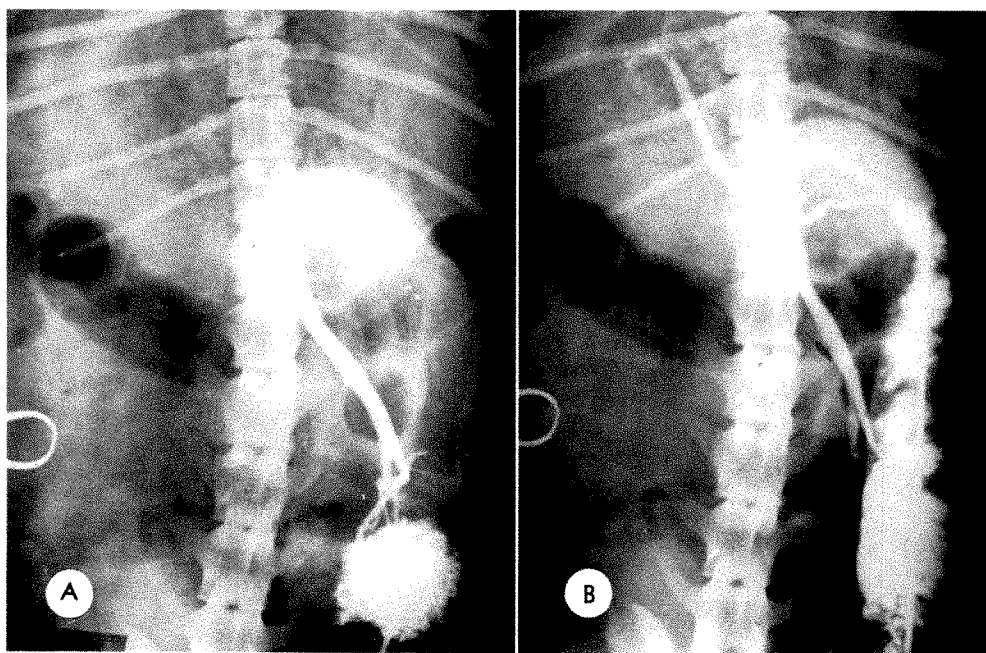


FIG. 4. (A) Injection into the lower pole of a dog's spleen using the conventional method.
(B) Injection made with the multi-hole needle.

The splenoportogram made with the conventional needle (Fig. 5) demonstrated 2 small vessels leaving the splenic shadow and converging retrogradely towards a larger vessel, which constituted the trunk of the splenic artery. With the multiple side-orifice needle (Fig. 6), 3 other vessels were visualized, one from the middle part of the spleen, another from the

lower pole, and a third one of much smaller caliber but forming into a thick vessel, which corresponded to the partially visible retrograde vessel on the first splenoportogram. There was no spillage of contrast medium into the peritoneal cavity.

After having ascertained surgically in several patients the innocuousness of the injection with the above-described needle,

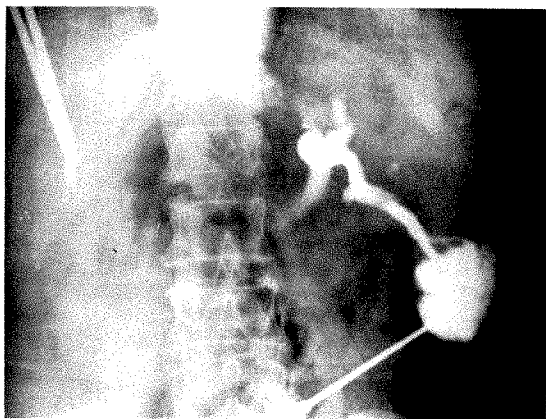


FIG. 5. Splenoportogram after injection of 20 cc. of contrast medium into the lower pole of the spleen with a conventional needle.

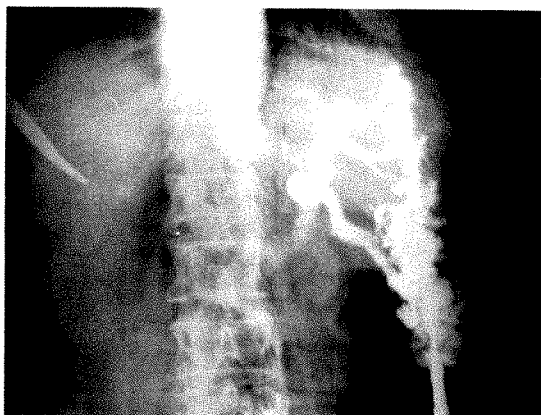


FIG. 6. Same injection in the same patient with multi-hole needle following the spleen's axis.

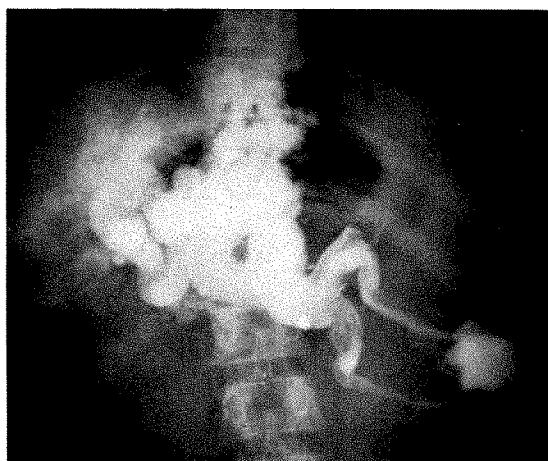


FIG. 7. Splenoportogram with injection into the spleen by the conventional method showing thrombosis of portal vein.

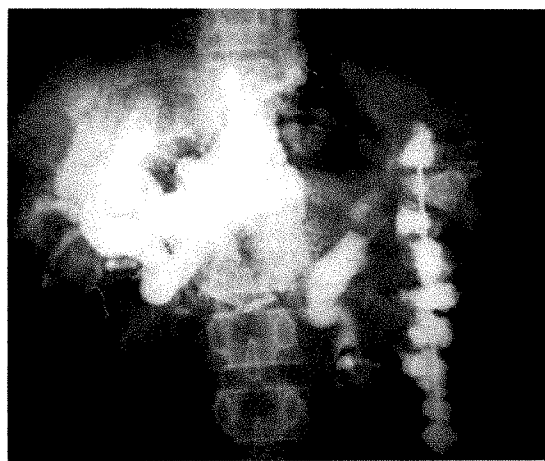


FIG. 9. Same patient as in Figures 7 and 8. Splenoportogram made 4 seconds after multi-hole needle injection.

we performed it through a transcutaneous puncture. In a patient with an enlarged spleen, a puncture was made in accordance with the conventional technique and then another puncture with the multiple side-orifice needle introduced into the spleen through its long axis. Forty cubic centimeters of urografin 76 per cent was used each time. Figure 7, the conventional study showed 2 veins leaving the splenic shadow and a rich collateral circulation due to thrombosis of the portal vein. The splenoportogram made with the multiple side-

orifice needle (Fig. 8) showed in addition to the 2 veins previously visualized, 4 more—3 leaving the upper pole and converging towards a larger vessel. A study made 2 seconds later (Fig. 9) demonstrated a much richer collateral circulation.

In order to determine the dimensions and shape of the spleen, so that a proper sized needle can be selected and injection made into the proper area, laminagraphy is performed prior to splenoportography.

SUMMARY

A new type of needle for use in splenoportography is described, which is sealed at the end and has a number of lateral holes equidistant on one side. Better visualization of the perisplenic circulation and, generally, of the collateral channels in cases of portal hypertension has been obtained.

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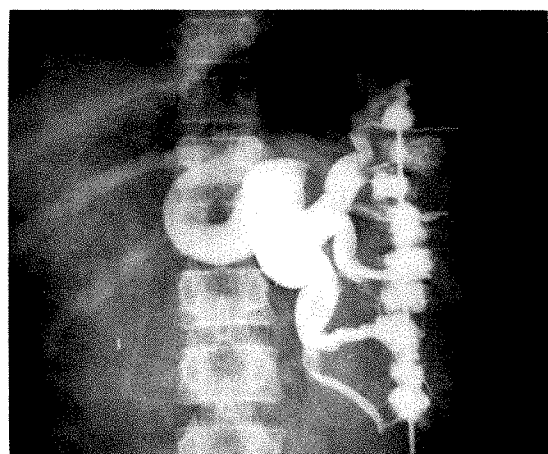


FIG. 8. Same patient as in Figure 7. Splenoportogram made 2 seconds after multi-hole needle injection.

THRESHOLD VISUAL PERCEPTION AND ITS RELATIONSHIP TO PHOTON FLUCTUATION AND SINE WAVE RESPONSE*

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IN 1948, Rose⁹ of the RCA Laboratories in Princeton proposed a statistical hypothesis to account for the thresholds of visual acuity and contrast perception observed at various levels of scene luminance. The following year, Sturm and Morgan¹¹ extended this theory to the field of fluoroscopy to predict the visual characteristics of ideal fluoroscopic screen intensification systems.

The hypothesis advanced by Rose is based on the fact that light is composed of discrete photons whose number in any given situation fluctuates randomly about some average value in accordance with well-known statistical principles. Such fluctuations arise because of the probabilistic nature of photonic processes. For example, when light of given intensity is projected on an observer's eye, a definite number of photons may be expected to reach and stimulate the retina in a given time interval. However, there is no certainty that precisely such a number will actually arrive. Indeed, if measurements are made, it will be found that the number of incident photons fluctuates from moment to moment and from region to region about some average value approaching the expected number. The situation is analogous to that which prevails when one tosses a coin. Although the probability of tossing a heads is 50 per cent, an experiment in which a coin is repeatedly tossed 10 times yields a total of 5 heads only occasionally; at other times, the number fluctuates randomly on either side of 5.

The random fluctuations which characteristically accompany all photonic pro-

cesses are superimposed on the regularly ordered variations of light intensity which constitute optical images. Such fluctuations, therefore, may be expected to interfere with the reproduction of these images and, in the case of the visual process, make their perception more difficult.

In presenting his hypothesis, Rose investigated the perception of a series of round dots of graded size and contrast, distributed on a field of uniform brightness. Such an array was chosen because visual images may be regarded as composites of large numbers of dot-like areas. Rose postulated that a given dot can be perceived only when the average difference in the number of photons reaching and stimulating the retina from the dot and from an equal area of the surrounding field during the storage time of the eye exceeds by several times the root-mean-square value of the statistical fluctuation in the number of photons from the dot in a similar time period; that is, dot perception may be expected to occur only when the dot contrast substantially exceeds the randomly fluctuating light intensity received from the dot.

The magnitude of the photon fluctuation which occurs at the retina in a particular situation is an inverse function of the number of photons involved in the visual process. By an analysis which need not be repeated here, Rose developed the following formula relating the angular size, α , expressed in minutes of arc, and the per cent contrast, C , of a dot which may be just perceived at a luminance of B foot-lamberts:

$$C^2 = 5(k^2/t\theta) \cdot (1/D^2B) \cdot (1/\alpha^2) \times 10^{-3}. \quad (1)$$

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Presented in part at the Second Colloquium on Radiologic Instrumentation, University of Chicago, April 20-24, 1964. Proceedings published by Charles C Thomas, Springfield, Ill., 1965.

In this expression, k is a proportionality factor having a value of approximately 5, t is the storage time of the eye in seconds, θ is the so-called quantum efficiency of the retina and D is the diameter of the observer's pupil in inches.

Equation 1 was modified somewhat by Sturm and Morgan for fluoroscopic conditions as follows:

$$C = (k/d)(4/\pi n\theta t)^{1/2} \times 10^2, \quad (2)$$

where n is the number of photons/mm.²/sec. prevailing at that stage of the fluoroscopic process where n reaches its lowest level and d is the diameter in mm. of a just perceptible dot when viewed at a distance of 20 cm.

Figure 1 illustrates the extent to which physiologic measurement confirms the Rose hypothesis. The broken lines show predicted values of threshold contrast plotted as a function of angular dot-size for scene luminances extending from 10^{-4} to 10 foot-lamberts. These data were obtained when the term, k^2/θ of equation 1, was given a value of 1,900. Also in Figure 1, are shown visual performance data obtained from measurements published by Rose and attributed to Blackwell.¹

It will be seen that predicted and measured values deviate substantially from each other at high luminance levels. To explain this, Rose suggested that the value of k^2/θ may be governed by scene luminance and hence the measured and predicted data might be brought into greater conformity if the value of k^2/θ should systematically increase as scene luminance increases. This suggestion has received some support recently from measurements of the temporal frequency response of the eye⁵ which indicate that the eye's temporal bandwidth is approximately threefold greater at high scene luminance than at low.

With further reference to Figure 1, it will be observed that substantial deviation between measured and predicted values also occurs at both high and low levels of dot contrast. This finding is more difficult to explain.

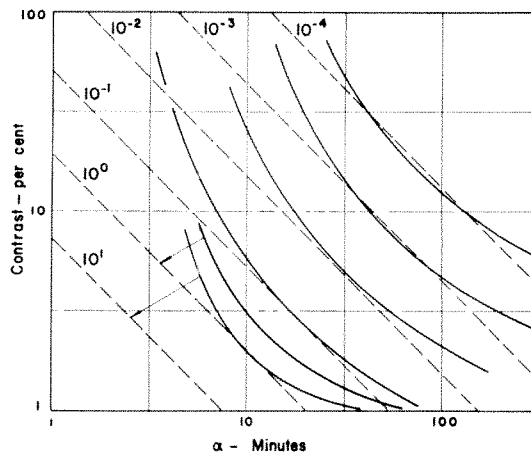


FIG. 1. Threshold contrast plotted as a function of image size, measured in terms of the angle subtended by the image on the retina, for disk-type test objects at levels of screen luminance ranging from 10^{-4} to 10 foot-lamberts. Broken lines are values predicted from equation 1. Solid curves are measured performance data, published by Rose from Blackwell data.

The disparity between predicted and measured values of visual performance, as expected from the Rose theory, is a matter of some concern. However, the concept that statistical photon fluctuation may be expected to interfere with visual performance and that the contrast of an image, if it is to be seen, must exceed this fluctuation by some definite factor is quite attractive. Indeed, it is of interest to note in Figure 1 the extent to which predicted and measured values systematically approach each other at least for limited ranges of threshold contrast.

The foregoing raises the question as to why the Rose hypothesis fails when it does. A partial answer to this question may perhaps be found in the visual performance data published by Sturm and Morgan¹¹ and reproduced in Figure 2. These data are similar to those presented in Figure 1, except that threshold contrast is plotted against dot diameter in millimeters and the data are restricted to those observed at scene luminances ranging from 10^{-2} to 10^{-4} foot-lamberts. It will be seen that the three curves closely resemble one another in form. Also, if one replots the data as a function of

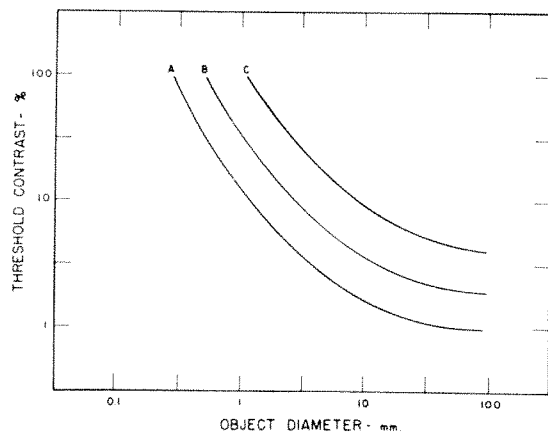


FIG. 2. Threshold contrast plotted as a function of image diameter for dot-type test objects viewed at a distance of 20 cm. Curve A is for a scene luminance of 10^{-2} foot-lambert; curve B, 10^{-3} foot-lambert and curve C, 10^{-4} foot-lambert.

reciprocal dot diameter and with the threshold contrast scale inverted as shown in Figure 3, the resultant curves are similar in configuration to the spatial modulation transfer functions of optical system photoreceptors.⁸ It will be recalled that such functions express the relationship between the relative response of a photoreceptor, when exposed to a sine wave test pattern, and the pattern's spatial frequency. This observation is of some interest because the images of dot test patterns, like all images, are sine wave composites. Furthermore, reciprocal dot diameter is dimensionally equivalent to and a closely related function of the spatial frequencies which comprise a dot's image. Finally, threshold contrast reflects the retina's response to these frequencies. Hence, it appears that visual perception is inversely related to the modulation transfer function of the visual system and that such a function should play an important role in the development of any mathematical model representing the system.

Another reason for the failure of the Rose hypothesis may perhaps be found in the methods used in the calculation of visual fluctuation levels. Photon fluctuation, when expressed as a per cent of the number of photons taking part in the visual process, is generally an inverse function of

the photon number. Therefore, because the number of photons comprising a visual image increases as image size becomes larger, Rose argued that for a scene of given luminance there is less fluctuation associated with a large image than with a small one. Superficially, this argument seems reasonable. However, it fails to take into consideration the fact that the eye possesses relatively broad frequency response characteristics in both time and space which cause it to see and be disturbed by fluctuations arising from elemental areas of the visual field which may be much smaller than the image under observation.

The problems associated with the calculation of visual fluctuation are analogous to those encountered in the calculation of noise in auditory systems. In the latter instance, noise is not a function of the pitch of an audible signal but of the sine wave response of the system. So too, in the visual process, one may expect that the analogous photon fluctuation is not governed by image size but by the sine wave response characteristics of the several components comprising the system. Photon fluctuation could be related to image size if the components of the visual process were capable of restricting their sine wave response characteristics to those just needed to record the images presently in view. However, the eye appears to have no

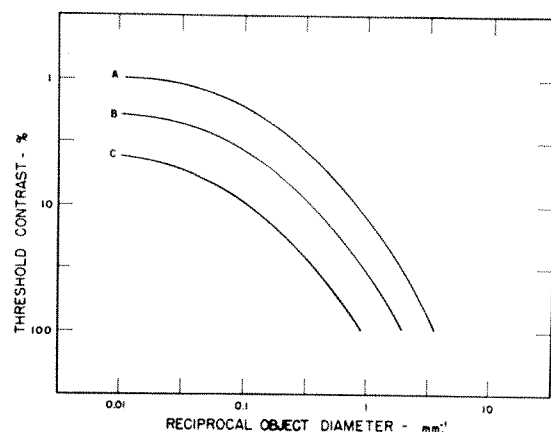


FIG. 3. Same data as in Figure 2 but with threshold contrast scale inverted and with abscissa indicating reciprocal image diameter.

such ability. For example, when a noisy television picture is observed, the scintillating background seems equally as bothersome to the perception of the larger images as it does to the smaller ones. It, therefore, seems clear that visual fluctuation should not be calculated from the size of the image under observation.

In view of the foregoing discussion, let us now turn our attention to the development of a mathematical model which in predicting the limits of visual perception takes into consideration the sine wave response characteristics of the eye and of associated optical components, when present, and which treats random fluctuation independently of image size.

RANDOM FLUCTUATION IN VISUAL SYSTEMS

A. DEFINITION OF TERMS

In the discussions which follow, a number of terms are used which, for the sake of clarity, are defined at the outset.

Photoreceptor. A surface composed of elements capable of reacting to an incident energy pattern (photons, electrons, etc.); e.g., the retina of the eye, photographic film, fluoroscopic screens, photoelectric surfaces.

Statistical unit (s. u.). A quantity counted statistically as an independent event in a quantized energy state of flux; e.g., photons, electrons, atoms, neural impulses or aggregates of any one of these acting as a unit.

Statistical transfer ratio, μ_s . The ratio of the number of statistical units produced by a photoreceptor as an output signal to the number of statistical units received by the photoreceptor; in the case of the retina, μ_s refers to the number of neural impulses produced by the rods or cones per incident photon.

Spatial frequency (ν_x , ν_y , or ν_z). The number of cycles per unit length of a pattern whose quantized energy flux density oscillates in one of the dimensions of space.

Temporal frequency (ν_t). The number of cycles per unit of time of a pattern whose quantized energy flux density oscillates as a function of time.

Passband. The range of frequencies transmitted by or reacting with an element of an optical system; e.g., an eye which responds to spatial frequencies between ν_1 and ν_2 cycle/mm. exhibits a passband of $\nu_2 - \nu_1$.

Modulation transfer function or sine wave response function, $A^s(\nu)$. A relationship which expresses the normalized response of a photoreceptor, when exposed to a sine wave test pattern, as a function of the spatial or temporal frequency of the pattern.

Contrast (C). The ratio of the root-mean-square value of the oscillating component of a pattern's energy flux density to the pattern's average energy flux density. In the case of a uniformly illuminated test object whose pattern varies sinusoidally in a single spatial dimension, object contrast, C_o , is equal to $0.7 (B_1 - B_2) / (B_1 + B_2)$, where B_1 and B_2 are maximum and minimum test-object luminances respectively.

Threshold contrast (C_T). The minimum perceptible contrast level.

Fluctuation contrast (C_N). The ratio of the root-mean-square value of the randomly fluctuating component of a pattern's energy flux density to the pattern's average flux density.

Noise. A synonym for fluctuation.

B. FLUCTUATION IN SINGLE PHOTORECEPTOR SYSTEMS

To determine the magnitude of the random fluctuation prevailing in a visual system, consider first a uniformly illuminated surface, $x-y$, composed of a large number of photoreceptive elements, which receives n photons in an incremental area, Δx , Δy , during a time interval, Δt (see Fig. 4). Because of the discontinuous nature of light, these photons may be expected to fluctuate about some average value, N , when sample measurements are made from time to time at various locations within the $x-y$ plane; that is,

$$\langle n \rangle = N, \quad (3)$$

where the brackets signify an average over an equilibrium ensemble.

The mean-square value of the fluctuation

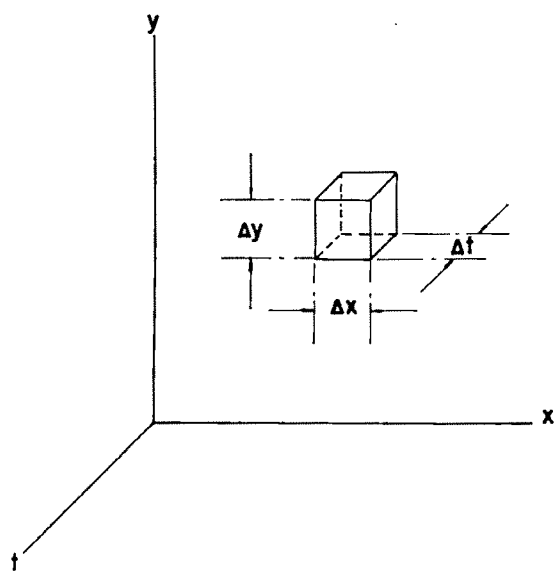


FIG. 4.

characteristics such that an element, $\Delta x \cdot \Delta y \cdot \Delta t$, is resolved with perfect clarity, whereas a just smaller element is not recorded at all. However, as is well known, optical systems do not exhibit these properties. Instead, their response to a series of progressively smaller elements shows gradual deterioration in accordance with their frequency response characteristics. Hence, a more satisfactory expression for fluctuation contrast must be sought.

Now optical systems are characteristically ergodic; that is, the fluctuation associated with an incremental element, $\Delta x \cdot \Delta y \cdot \Delta t$, is the same whether one samples in the x -, y -, or t -axis or in any combination of the three. Therefore, by Fourier analysis, each of the elemental dimensions in equation 6 may be replaced by an appropriate partial integral as follows:

may be shown statistically to be

$$\langle (n - N)^2 \rangle = \langle dn^2 \rangle = N. \quad (4)$$

Now, if \bar{n} is the average number of photons/mm.²/sec. received by the x - y plane, then

$$\langle dn^2 \rangle = \bar{n} \Delta x \cdot \Delta y \cdot \Delta t. \quad (5)$$

From the definition of fluctuation contrast given heretofore, equation 5 indicates

$$1/\Delta x = 2 \int |A^t(\nu_x)|^2 \delta \nu_x \quad (7a)$$

$$1/\Delta y = 2 \int |A^t(\nu_y)|^2 \delta \nu_y \quad (7b)$$

$$1/\Delta t = 2 \int |A^t(\nu_t)|^2 \delta \nu_t, \quad (7c)$$

where $A^t(\nu_x)$, $A^t(\nu_y)$ and $A^t(\nu_t)$ are the modulation transfer functions of the photo-receptor in the x -, y -, and t -dimensions respectively. Consequently,

$$C_N^2 = \frac{\iiint \delta C_N^2}{\bar{n}} = \frac{2 \int |A^t(\nu_x)|^2 \delta \nu_x \cdot 2 \int |A^t(\nu_y)|^2 \delta \nu_y \cdot 2 \int |A^t(\nu_t)|^2 \delta \nu_t}{\bar{n}}. \quad (8)$$

that

$$C_N^2 = \frac{\langle dn^2 \rangle}{(\bar{n} \cdot \Delta x \cdot \Delta y \cdot \Delta t)^2} = \frac{1}{\bar{n} \cdot \Delta x \cdot \Delta y \cdot \Delta t}. \quad (6)$$

For equation 6 to be useful in the calculation of fluctuation contrast, the photo-receptor surface must have sharply defined limits of resolution in both the space and time domains; *i.e.*, the surface must have

The partial integrals of equations 7a-7c and of equation 8 represent sharply defined passbands, spatial and temporal, equivalent from the standpoint of noise generation to the broader and less sharply defined passbands to which the photo-receptor is responsive. For this reason, these integrals are often referred to as noise-equivalent-passbands and denoted respectively by the symbols, ν_{ex} , ν_{ey} , ν_{et} . Hence,

equation 8 may be written

$$C_{Nr} = \frac{2\nu_{ex} \cdot 2\nu_{ey} \cdot 2\nu_{et}}{\bar{n}} \quad (8a)$$

Many photoreceptors are isotropic in the x - and y -dimensions. Under these circumstances, $\nu_{ex} = \nu_{ey}$ and equation 8a may be simplified to

$$C_{Nr} = 2\nu_{ex} \cdot (2\nu_{et}/\bar{n})^{1/2} \quad (8b)$$

If the surface illustrated in Figure 4 is the retina of the eye, the observed fluctuation contrast is somewhat greater than that indicated by equation 8b because only $\bar{n}\mu_s$ of the incident photons produce neural impulses; hence, the retinal fluctuation contrast, C_{Nr} , is given by the equation

$$C_{Nr} = 2\nu_{ex} \cdot (2\nu_{et}/\bar{n}\mu_s)^{1/2} \quad (8c)$$

where the subscripts, r , indicate that the noise-equivalent-passbands are specifically those of the retina.

It is usually convenient to express the illumination on the retina in terms of scene luminance instead of \bar{n} . If a value of 1.4×10^{11} photon/mm.²/sec. is taken as equivalent to a luminance of 1 foot-lambert and a value of 17 mm. as the distance between the second nodal point of the eye lens and the retina, it may be shown by fundamental optical principles that

$$\bar{n} = 1.2 \times 10^8 \cdot BD^2T, \quad (9)$$

where B is scene luminance in foot-lamberts, D is the diameter of the pupil in mm. and T is the transmittance of the eye. When equation 9 is substituted in equation 8c

$$C_{Nr} = 2.6 \nu_{ex} \cdot (\nu_{et}/B\mu_s D^2 T)^{1/2} \times 10^{-4}. \quad (10)$$

Schade¹⁰ has investigated the spatial noise-equivalent-passband, ν_{etr} , of the retina at various levels of scene luminance and values of this parameter, taken from his work, are listed in column 4 of Table I. It perhaps should be pointed out that the passband of the retina normally extends downward to a frequency of 0 cycles/mm. However, the brain by certain feedback mechanisms suppresses retinal signals having frequencies below a few cycles/mm. Hence, the effective values of ν_{etr} are slightly less (a few per cent) than those tabulated.

The amplitude sensitivity of the eye, measured with sinusoidal time-dependent stimuli has recently been studied by Kelly.⁵ From these data, the eye's temporal noise-equivalent-passband, ν_{etr} , may be readily calculated if one assumes that the eye's temporal modulation transfer function is directly related to its temporal amplitude sensitivity. Values of ν_{etr} , calculated on this assumption, are listed in column 5 of Table I.

The statistical transfer ratio, μ_s , of the retina is a function of (a) the fractional light absorption of the rods and cones and (b) the number of neural impulses generated per absorbed photon. These factors have been studied extensively by a number of workers and it is now generally believed that the photon-impulse conversion efficiency of the rods is close to unity.¹² A similar efficiency is probably also exhibited by

TABLE I
EVALUATION OF RETINAL FLUCTUATION CONTRAST, C_{Nr}

Scene Luminance (foot-lamberts)	Pupil Diameter (mm.)	\bar{n} photons/mm. ² /sec.	ν_{exr} cy./mm.	ν_{etr} cy./sec.	C_{Nr}
300	2.5	3.9×10^{10}	90	22	6.1×10^{-3}
20	3.4	4.9×10^9	66	19.5	1.15×10^{-2}
1	4.3	3.8×10^8	40	14.5	2.2×10^{-2}
10^{-1}	5.1	5.4×10^7	25	9.25	2.9×10^{-2}
10^{-2}	5.7	6.8×10^6	16	8.0	4.9×10^{-2}
10^{-3}	6.3	8.4×10^5	11	7.5	9.4×10^{-2}
10^{-4}	6.7	9.5×10^4	9	7.5	2.3×10^{-1}

the cones.¹⁰ The fractional absorption of the rods seems to be near 0.35 when the retina is illuminated with white light. A somewhat higher value may be applicable to the cones.

The transmittance of the eye's ocular media has been studied by Ludvigh and McCarthy⁶ and has been shown to have a value close to 0.5 through most of the spectrum above a wavelength of 440 millimicrons. When such a value is substituted in equation 10 together with a value of 0.35 for μ_r , the fluctuation contrast of the retina, C_{Nr} , may be readily determined (see column 6, Table I).

It will be observed that for a range of scene luminance extending from 10^{-4} to 3×10^3 foot-lambert, C_{Nr} varies only by a factor of about 40:1. This remarkable performance is achieved by the combination of a pupil whose area is capable of changing by almost a factor of 10 and by the inclusion in the retina of two types of photoreceptive elements, the rods and cones, which exhibit widely different sine wave response characteristics in the time and space domains.

C. FLUCTUATION IN VISUAL SYSTEMS WITH MULTIPLE PHOTORECEPTORS

Many visual systems include one or more photoreceptors in addition to the observer's retina. For example, in x-ray fluoroscopy, one may count as many as 7 such surfaces in a system which incorporates an image amplifier and associated television apparatus.

equation

$$C_{NT}^2 = C_{N1}^2 + C_{N2}^2 + \cdots C_{Nn}^2 + \cdots C_{Nr}^2, \quad (11)$$

where the subscripts refer to the 1st, 2nd, —nth—and retinal photoreceptors respectively.

In general, the fluctuation contrast, appearing at the retina as a consequence of any given photoreceptor, may be derived by methods similar to those used in the derivation of the fluctuation contrast generated within the retina, itself; that is, from a determination of the number of statistical units transmitted per unit area, per unit time by the photoreceptor and from an evaluation of appropriate spatial and temporal noise-equivalent-passbands. It should be pointed out, however, that the passbands which are characteristically those of the photoreceptor, may not necessarily be those which should be employed in these calculations. The reason for this is that the modulation transfer functions of succeeding photoreceptors may restrict system performance below that expected from the characteristics of the given photoreceptor alone and thereby may diminish fluctuation contrast values. Hence, one must use composite transfer functions and noise-equivalent-passbands which reflect the combined characteristics of all photoreceptors included between the given photoreceptor and the retina; that is, the fluctuation contrast, C_{Nn} , due to the n th photoreceptor of an isotropic system is

$$C_{Nn} = \frac{2 \int |A_{cn}^t(\nu_x)|^2 \delta \nu_x \cdot \left[2 \int |A_{cn}^t(\nu_t)|^2 \delta \nu_t \right]^{1/2}}{\bar{n}_n^{1/2}} = 2 \nu_{secn} \cdot (2 \nu_{atcn} / \bar{n}_n)^{1/2}, \quad (12)$$

Because the response of a photoreceptor is probabilistic, fluctuation is generated by each photoreceptor stage. It may be shown statistically that the total fluctuation contrast, C_{NT} , of a visual system is related to the fluctuation contrast due to each of the system's individual photoreceptors by the

where the subscript, c , denotes that the several transfer functions and noise-equivalent-passbands are composite functions and passbands.

Schade has shown that, to a close approximation, the composite spatial noise-equivalent-passband of a photoreceptor

TABLE II
FLUCTUATION CONTRAST IN X-RAY FLUOROSCOPY

System	Single Screen	Image Amplifier	Image Amplifier	Image Amplifier
Exposure rate (r/sec.)	3.5×10^{-4}	3.5×10^{-4}	3.5×10^{-4}	3.5×10^{-4}
Screen absorption	0.5	0.25	0.25	0.25
Absorbed x-ray exposure rate (photons/mm ² /sec.)	3.5×10^4	1.75×10^4	1.75×10^4	1.75×10^4
Luminance (foot-lamberts)	10^{-3}	3	3	3
Viewing distance (cm.)	20	50	100	200
Magnification (retina/screen)	8.5×10^{-2}	3.4×10^{-2}	1.7×10^{-2}	8.5×10^{-3}
ν_{exn} (cy./mm.)	0.82	0.6	0.6	0.6
$\nu_{\text{ex}(r+L)}$ (cy./mm.)	6	23	23	23
$\nu_{\text{ex}(r+L)} \cdot M$ (cy./mm.)	0.51	0.78	0.39	0.19
ν_{exon} (cy./mm.)	0.45	0.48	0.32	0.18
ν_{etn} (cy./sec.)	300	130	130	130
ν_{etr} (cy./sec.)	7.5	16.5	16.5	16.5
ν_{eton} (cy./sec.)	7.5	16.5	16.5	16.5
C_{Nr}	1.85×10^{-2}	4.2×10^{-2}	2.7×10^{-2}	1.5×10^{-2}
C_{Nr}	9.4×10^{-2}	1.9×10^{-2}	1.9×10^{-2}	1.9×10^{-2}

may be calculated from the equation

$$\nu_{\text{exon}}^{-2} = \nu_{\text{exn}}^{-2} + (\nu_{\text{ex}(n+1)} \cdot M_{(n+1)})^{-2} + \dots (\nu_{\text{etr}} \cdot M_r^{-2}), \quad (13)$$

where the terms in M represent the magnification present between the n th photoreceptor and the photoreceptor indicated by the subscript associated with M ; these terms are, of course, necessary to bring all of the spatial frequency values to a common standard of reference. The formula corresponding to equation 13 in the time domain is

$$\nu_{\text{eton}}^{-2} = \nu_{\text{etn}}^{-2} + \nu_{\text{et}(n+1)}^{-2} + \dots \nu_{\text{etr}}^{-2}. \quad (13a)$$

It will be evident from equation 11 that the total fluctuation contrast of a visual system is largely determined by that photoreceptor which introduces the greatest individual fluctuation contrast. Equations 12, 13 and 13a therefore provide the means whereby C_{Nr} may be readily calculated, even for very complex visual systems.

D. FLUCTUATION CONTRAST IN X-RAY SYSTEMS

It has been mentioned previously that x-ray fluoroscopic systems characteristically include several photoreceptors. Re-

gardless of system complexity, maximal fluctuation contrast frequently arises either within the x-ray fluorescent screen or within the observer's retina. It, therefore, may be of some interest to calculate the values of fluctuation contrast associated with the screen of a typical fluoroscope and to compare them with appropriate values of C_{Nr} . Four examples of such calculations are shown in Table II.

The first example applies to a simple fluoroscope equipped with a conventional viewing screen and observed from a distance of 20 cm.; the remaining three are for a fluoroscopic installation equipped with a directly viewed image amplifier, having an intensification of 3×10^3 , and observed at effective distances of 50, 100 and 200 cm. By the term "effective distance" is meant a distance such that the angle subtended by the amplifier's viewing screen to the eye is identical to that which would occur if the amplifier included no magnification.

In the several examples cited, an x-ray exposure rate of 3.5×10^{-4} r/sec. is used; this rate is typical of conventional practice. The numbers of absorbed x-ray photons/mm.²/sec. corresponding to this rate were calculated from the absorption characteristics of the two x-ray photoreceptors

and from appropriate tables equating exposure rates and x-ray photon flux densities.⁷

Values of the spatial and temporal noise-equivalent-passbands (ν_{esn} and ν_{etr}) listed for screen and image amplifier were derived from modulation transfer data recently acquired in this laboratory. Corresponding values for the eye, including the lens as well as the retina, are from Schade (spatial passbands) and from calculations made from data published by Kelly (temporal passbands); these data are listed in Table III. Values of retinal fluctuation contrast, C_{Nr} , are from Table I.

The fluctuation contrasts of the x-ray fluorescent screen and retina, listed at the bottom of Table II, are noteworthy from several points of view. It will be observed that in conventional fluoroscopy, the fluctuation contrast of the retina is substantially greater than the fluctuation contrast of the screen. Indeed, the latter is so small that it may be predicted that an observer should be unable to perceive the screen's scintillation pattern. When the eye is aided by an image amplifier, however, the situation is quite different. Here, at a 50 cm. viewing distance, C_{Nn} is substantially greater than retinal fluctuation contrast, and hence the screen's scintillation pattern should be readily apparent. As the viewing distance is increased, C_{Nn} diminishes with an expected reduction in perceptible scintillation. Finally, at long viewing distances, C_{Nn} becomes smaller than C_{Nr} and scintillation patterns should no longer be visible. As is well known to all users of fluoroscopic equipment, these predictions are faithfully borne out in practice.

CONTRAST SENSITIVITY OF VISUAL SYSTEMS

It has been pointed out earlier in this paper that an image projected upon the retina may be expected to be seen only when its contrast, C_r , is equal to or exceeds some multiple of the fluctuation contrast; that is,

$$C_r \geq kC_{Nr}, \quad (14)$$

TABLE III

NOISE-EQUIVALENT-PASSBANDS OF RETINA,
INCLUDING COMPOSITE OF RETINA AND
EYE LENS (FROM SCHADE¹⁰ AND KELLY⁶)

Scene Luminance (foot-lamberts)	ν_{esr} cy./mm.	$\nu_{es(r+L)}$ cy./mm.	ν_{etr} cy./sec.
10^3	95	35	23
10^2	80	31	21
10^1	63	27	18.5
10^0	40	18	14.5
10^{-1}	25	14	9.25
10^{-2}	16	9	8.0
10^{-3}	11	6	7.5
10^{-4}	9	4.5	7.5

where k is a constant, the so-called threshold signal-to-noise contrast ratio.

When the scene under observation is a test object bearing a sinusoidal pattern in the space domain, the relationship between retinal contrast and test object contrast is

$$C_r = |A_{cr}^*(\nu_s)| \cdot C_o, \quad (15)$$

where $A_{cr}^*(\nu_s)$ is the composite spatial modulation transfer function of the complete visual system. As before, the term, "composite" spatial modulation transfer function, means the product of the functions of the several elements of the visual system, including the retina and lens of the eye and any other system components which may limit system response. This product, again, may be computed only after all frequency values have been brought to a common standard of reference to adjust for any magnification present in the system. In this connection it is usually most convenient to use the frequency of the test object or of the image appearing at the retinal surface as the standard of reference.

When equations 14 and 15 are combined, visual performance expressed in terms of threshold test object contrast, C_{To} , is given by the formula

$$C_{To} = kC_{Nr} / |A_{cr}^*(\nu_s)|. \quad (16)$$

As previously indicated C_{Nr} is usually equal to C_{Nn} . Hence, from equation (12), when

sinusoidal test objects are observed in isotropic systems, the conditions for threshold visual perception may be expressed quantitatively by the formula

$$C_{T_0} = [2k\nu_{\text{axon}} / |A_{\text{or}}^*(\nu_s)|] \cdot [2\nu_{\text{aton}} / \tilde{n}_n]^{1/2}. \quad (17)$$

Equations 16 and 17 constitute a mathematical model with which the threshold contrast of sinusoidal test objects may be predicted in complex as well as in simple visual systems. These equations, as is evident from their derivation, may also be used to predict the threshold preception of *other types of test object* if the modulation transfer function, $|A_{\text{or}}^*(\nu_s)|$, for sinusoidal patterns is replaced by an appropriate transfer function which gives the composite response of the visual system in terms of the spatial characteristics of the test object in question.

The value of k in equations 16 and 17 may be determined from measurements of threshold test object contrast made under conditions where $C_{NT} = C_{Nr}$ and $|A_{\text{or}}^*(\nu_s)| = 1.0$; that is, where threshold contrast is governed entirely by the retina and where the sine wave contrast sensitivity of the eye is maximal. Under these circumstances, k is simply equal to C_{T_0}/C_{Nr} .

At the present time, only limited data on the eye's sine wave contrast sensitivity have been published.⁴ However, where such data are not available, the needed values of C_{T_0} may be obtained from threshold contrast measurements made with dot test-patterns if one assumes that the minimum values of threshold contrast (*i.e.*, maximum values of contrast sensitivity), obtained with these patterns, are similar to those obtained with sinusoidal test objects. In cases where corresponding data are available,^{1,4} this assumption appears to be generally valid if contrast values are expressed in accordance with the definitions given earlier in this paper.

Column 2 of Table IV lists threshold test object contrast values for several levels of scene luminance, obtained from contrast sensitivity measurements reported by DePalma and Lowry,⁴ Blackwell,¹ and Sturm

TABLE IV
EVALUATION OF THRESHOLD SIGNAL-TO-NOISE
CONTRAST RATIO, k

Scene Luminance (foot- lamberts)	Threshold Contrast, C_{T_0}	Fluctuation Contrast, C_{Nr}	k
300	1.1×10^{-3}	6.1×10^{-3}	0.19
20	1.4×10^{-3}	1.15×10^{-2}	0.12
1	3.5×10^{-3}	2.2×10^{-2}	0.16
10^{-1}	4.5×10^{-3}	2.9×10^{-2}	0.15
10^{-2}	6.5×10^{-3}	4.9×10^{-2}	0.13
10^{-3}	1.4×10^{-2}	9.4×10^{-2}	0.15
10^{-4}	3.0×10^{-2}	2.3×10^{-1}	0.13

and Morgan.¹¹ Column 3 lists corresponding values of C_{Nr} , taken from Table 1. Values of k are tabulated in column 4. It will be observed that k is unusually constant over the broad range of scene luminance studied. One should perhaps expect this since the computational processes performed by the brain on the retinal signals are not likely to be different at one scene luminance from another. However, the constancy of k as shown in Table IV is noteworthy.

Another characteristic of k is its very small size. This parameter has a value of the order of 5 when calculated in accordance with the Rose hypothesis. The smaller values reported here are due to several factors. First, fundamental differences in the derivations of equations 1 and 17 are partially responsible. Second, the definition of contrast employed in this paper yields contrast values approximately one-half those obtained from the definition used by Rose. Hence, previously published data on k must be multiplied by a factor of 0.5 to make them comparable to the data shown in Table IV. Finally, Rose in making his calculations of visual performance assumed a storage time for the eye of 0.2 seconds. This implies that the eye's temporal noise-equivalent-passband is of the order of 2.5 cycles/second. In this paper, however, values of 7.5 to 23 cycles/second, based on recent work by Kelly, were used.

This causes an additional 2- to 3-fold reduction in k -values. Parenthetically, there is no intention here to imply that the Kelly data are correct and previously held values of the eye's storage time are not. Although Kelly's work was performed painstakingly with modern techniques and hence seems reliable, the purpose of this discussion is only to indicate the reasons why the values of k in Table IV are relatively small. It will be apparent that the second and third reasons just cited are merely technical and although their influence is substantial, they do not reflect conceptual differences between the Rose hypothesis and that presented in this paper.

Coltman and Anderson² have recently published the results of a series of experiments from which the value of k may be estimated under conditions where the transmittance of the eye and the statistical transfer ratio of the retina are not involved in the calculation. This is of particular interest because the investigation provides an independent check on the values listed in Table IV.

In these experiments, threshold contrast was measured from a series of sinusoidal test patterns, presented on the face of a television monitor. The television system included sinusoidal and noise generators with appropriate controls by which the two signal levels could be varied to provide threshold conditions. At all times, however, the noise signals were maintained at a sufficiently high level so that scintillation appearing on the television monitor overrode fluctuation generated at the retina.

Observations were made through a broad range of viewing distance and test pattern frequency. At each viewing distance, the pattern frequency was adjusted to that level at which perception occurred with a minimum signal-to-noise ratio. S/N measurements were made in terms of the signal-to-noise current ratio prevailing in the television system. They may be converted to values of k by the following expression (see appendix 1):

$$k = \frac{(I_s/I_n) \cdot (\mu_h \mu_v \nu_{sta})^{1/2}}{2\nu_{szob} \cdot (A \cdot \nu_{stob})^{1/2}}, \quad (18)$$

where I_s/I_n is the measured signal-to-noise current ratio, μ_h and μ_v are the horizontal and vertical sweep efficiencies of the television monitor respectively, ν_{sta} is the television amplifier's temporal noise-equivalent-passband, ν_{szob} and ν_{stob} are the system's composite spatial and temporal noise-equivalent-passbands, respectively, and A is the area of the monitor's viewing surface.

Coltman and Anderson² carried out their measurements with a television monitor 11 inches wide and exhibiting an average luminance of 40 foot-lamberts. At such a luminance, DePalma and Lowry⁴ have shown that maximal contrast sensitivity occurs at a spatial frequency of about 13 cy./mm. when the viewing distance is 56 inches. With such a viewing distance, a field, 11 inches wide, projects a 3.4 mm. image on the retina. Hence, maximal contrast sensitivity occurs when the field includes $3.4 \times 13 = 44$ cycles. Under these circumstances, Coltman and Anderson obtained a value of 0.037 for I_s/I_n .

In Table V are listed pertinent data, needed for the calculation of k from the Coltman-Anderson experiments. The terms, ν_{sza} and ν_{szb} , refer to the spatial noise-equivalent-passbands of the television amplifier and kinescope beams respectively. The first was calculated from the formula

$$\nu_{sza} = \nu_{sta} \cdot \mu_h / \nu_h \cdot w, \quad (19)$$

where ν_h is the horizontal sweep frequency of the monitor and w is the width of the monitor's viewing surface. ν_{szb} was calculated from the formula

$$\nu_{szb} = \kappa / L, \quad (20)$$

where L is the cross-section of the kinescope beam and κ is a proportionality constant. For a beam having the characteristics of a perfect aperture, κ has a value approaching 0.5. It is unlikely to have a value greater

than 0.3 for beams of commercial kine-scopes, however.

It will be observed from Table v, that the threshold signal-to-noise contrast ratio, k , determined from Coltman-Anderson data, has a value of 0.11. Although somewhat lower than the values listed in Table iv, it must be regarded as being in good agreement with them particularly in view of the many sources of data from which the calculations in Table iv were made.

DISCUSSION

The hypothesis developed in preceding sections of this paper and expressed in equations 16 and 17 postulates that threshold visual perception is governed by (1) the prevailing fluctuation contrast and (2) the visual system's response to the spatial frequencies included within the patterns under observation. It further proposes that fluctuation contrast is determined by the system's sine wave response characteristics, both spatial and temporal, and the number of statistical units (photons, electrons, neural impulses, etc.) taking part in each of the system's several stages. It suggests that the size and shape of an image affect threshold perception by virtue of their control of the image's spatial frequencies; it is noteworthy, however, that image size is not expected to exert an influence on fluctuation contrast.

It perhaps is of some interest to examine the similarities and differences of this hypothesis and that proposed by Rose (equations 1 and 2). First, it will be observed that both hypotheses indicate that threshold contrast may be reduced, and hence visual perception improved, by an increase in the quantized energy flux density (e.g., scene luminance, x-ray intensity, etc.) delivered to the one or more photo-receptors of the visual system. Second, the term representing the storage time of the eye in the Rose formulae is replaced by a term depicting the system's temporal noise-equivalent-passband in equation 17. Finally, and of great importance, the term

TABLE V

EVALUATION OF k FROM COLTMAN-ANDERSON DATA.

Monitor Luminance	40 foot-lamberts
Monitor Width (w)	2.8×10^3 mm.
Monitor Aspect Ratio	4:3
Monitor Viewing Area (A)	6×10^4 mm. ²
Monitor Beam Cross- Section (L)	0.42 mm.
Amplifier Bandpass (ν_{sta})	5×10^6 cy./sec.
Horizontal Sweep Frequency (ν_h)	1.575×10^4 cy./sec.
Horizontal Sweep Efficiency (μ_h)	0.85
Vertical Sweep Efficiency (μ_v)	0.95
Viewing Distance	1.3×10^3 mm.
Magnification (retina/ screen)	1.3×10^{-2}
$\nu_{as(r+L)}$	30 cy./mm.
$\nu_{as(r+L)} \cdot M$	0.4 cy./mm.
ν_{exc}	0.95 cy./mm.
ν_{exc}	0.70 cy./mm.
ν_{exc}	0.32 cy./mm.
ν_{exc}	20 cy./sec.
I_s/I_n	0.037
k	0.11

representing the dimensions of the image under observation in equations 1 and 2 is replaced by two terms in equation 17: (a) one denoting the composite spatial noise-equivalent-passband of the system and (b) one representing the system's composite modulation transfer function. It is the use of these latter terms that causes predicted values of visual performance to conform closely to measured values over a broad range of scene luminance, test object contrast and pattern frequency.

Equation 17 may be expected to be useful in the evaluation of many complex visual systems including those encountered in x-ray fluoroscopy and radiography. For example, curve A in Figure 5 illustrates the predicted relationships prevailing between threshold contrast and test object frequency for conventional fluoroscopy when the screen has a luminance of 10^{-3} foot-lambert (abdominal fluoroscopy) and is observed at a distance of 20 cm.

Also shown in Figure 5 are the threshold

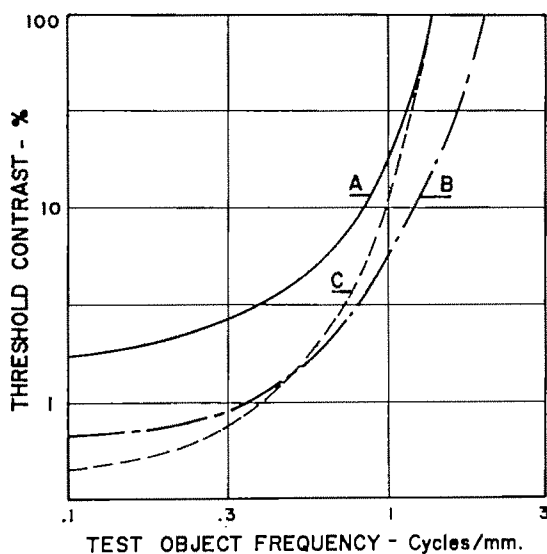


FIG. 5. Predicted values of threshold contrast prevailing during x-ray fluoroscopy when a conventional fluoroscopic screen is observed at a distance of 20 cm. (curve A); and a typical image amplifier, having a gain of 3,000 \times , is observed at effective viewing distances of 50 cm. (curve B) and 100 cm. (curve C). Data are for conditions where x-ray screen receives an exposure rate of 3.5×10^{-4} r/sec.

contrast levels to be expected when the eye is aided by a typical image amplifier having an intensification factor of 3,000 times and used at effective viewing distances of 50 cm. (curve B) and 100 cm. (curve C). Values of the composite noise-equivalent-passbands employed in their calculation are from data shown in Table II. The composite spatial modulation transfer functions were calculated from data for the eye, published by Schade and from data measured in this laboratory for the fluoroscopic screen and image intensifier. For all curves an exposure rate of 3.5×10^{-4} r/sec. has been assumed.

It will be observed that at short viewing distances, the amplifier may be expected to provide a substantial advantage over the conventional fluoroscopic screen at all spatial frequencies. As viewing distance increases, however, the advantage should narrow substantially, particularly at high spatial frequency values.

Figure 6 predicts the performance of several types of image amplifier viewed under conditions in which the composite spatial modulation transfer function of the fluoroscopic system is limited by the image amplifier itself. Curve A, section 1, represents the visual performance to be expected from a typical image amplifier operated at an exposure rate of 3.5×10^{-4} r/sec. Curve B shows the threshold performance that would prevail if the image amplifier's passband in the space domain were increased by a factor of 2. It will be of some interest to note that, at low spatial frequencies, the level of threshold contrast is higher (*i.e.*, performance is poorer) for the image amplifier having the improved resolution. This, however, is to be expected because greater resolution is always accompanied by an increase in the width of the system's noise-equivalent-passband. It should be pointed out that this loss in performance at low spatial frequencies is more than offset by an improved performance at higher frequencies (*i.e.*, in the region of fine detail).

The problem of increased contrast fluctuation occurring in image amplifiers with improved resolution may be circumvented by an increase in the exposure rate applied to the amplifier. This effect is shown in section 2 of Figure 6, where the two amplifiers are examined under conditions where the exposure rate applied to the improved unit is 4 times greater than that used with the conventional amplifier. Under these conditions, the fluctuation contrasts of both amplifier systems are identical and an improved visual performance may be expected from the better amplifier at all frequency levels.

As indicated in equation 12, fluctuation contrast may be decreased by a diminution in the temporal frequency response of the system. Curve B, section 3, illustrates the threshold contrast performance to be expected from an image amplifier whose temporal noise-equivalent-passband is one quarter of that exhibited by the eye. Curve A again represents the performance of a

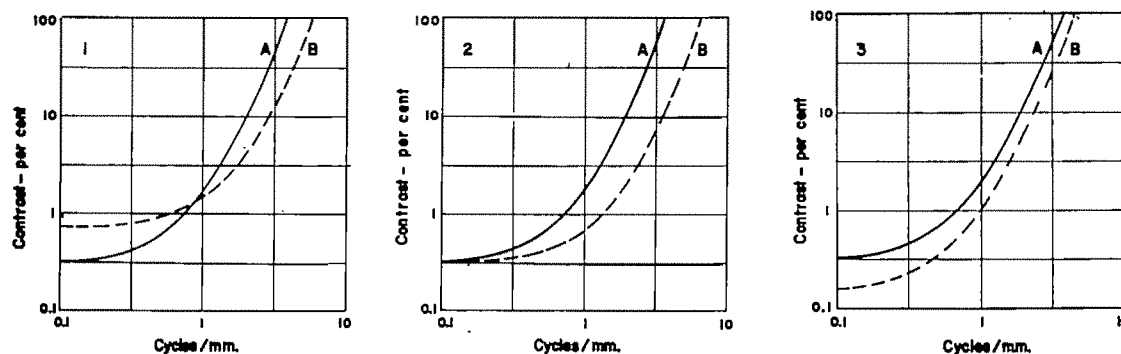


FIG. 6. Predicted values of threshold contrast plotted against test object frequency obtained with several types of image amplifier under conditions where the composite spatial modulation transfer function of the visual system is governed entirely by image amplifier characteristics. Curve A, all sections: typical image amplifier. Curve B, section 1: large screen amplifier whose spatial passband is $2\times$ that of typical amplifier. Curve B, section 2: same as curve B, section 1, except that exposure rate is increased $4\times$. Curve B, section 3: amplifier whose temporal passband is $0.25\times$ that of the retina. Unless otherwise specified, all data are for exposure rate of 3.5×10^{-4} r/sec.

typical amplifier. It will be seen that visual performance is improved at all spatial frequencies. Of course, the benefits gained from a curtailed temporal frequency response are achieved only at the expense of blurring of moving structures. Often, such blurring cannot be tolerated.

The data presented in Figures 5 and 6 have been generally known to most radiologists in a qualitative sense for some time. For example, one frequently finds that the performance of an image amplifier may be quite disappointing when compared to that of conventional fluoroscopy if the viewing distances employed with the image amplifier are excessive. Also, when an image amplifier of improved resolution is compared to a more conventional type, the benefits of this resolution are not fully achieved unless there is a corresponding increase in the exposure rate applied to the amplifier. Finally, it is well known that the visual performance obtained with an amplifier system whose temporal frequency response is limited (e.g., by the use of a vidicon television system) may appear to be superior to that of a system in which the temporal response is not curtailed. However, this improvement prevails only for stationary images. When structural mo-

tion is present, visual performance deteriorates rapidly with increasing rates of movement.

Equation 17 has extensive application in the solution of many problems associated with the prediction of the performance of visual systems. Its only major limitation currently is the absence of frequency response data on many of the elements comprising today's complex systems. In the field of radiology, considerable effort is being made in a number of laboratories to gain the needed information on films, screens, image amplifiers, television systems and cinefluorographic apparatus. As these data become available, rather full evaluation, both on a comparative and absolute basis, should be possible for an increasing number of fluoroscopic and radiographic designs by means of the relationships developed in this paper.

SUMMARY

A new model to predict the performance of complex visual systems, including those of radiography and fluoroscopy, has been developed. It takes into consideration a number of important characteristics of the visual process not treated in previous models. Several examples of the model's

use in the evaluation of the performance of fluoroscopic systems are given.

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APPENDIX I

CALCULATION OF THRESHOLD SIGNAL-TO-NOISE CONTRAST RATIO FROM COLTMAN-ANDERSON DATA

The noise current of the Coltman-Anderson television system was produced by a saturated diode operating into a broadband a.c. amplifier. At the diode, this current, i_n , may be shown by classic statistical theory to be

$$i_n = (2 e i v_{eta})^{1/2}, \quad (1.1)$$

where i is the average diode current, e is the charge on the electron and v_{eta} is the temporal noise-equivalent-passband of the amplifier. If the a.c. gain of the amplifier is g_a , the noise current, I_n , appearing at the amplifier output and impressed on the system's monitor is

$$I_n = g_a (2 e i v_{eta})^{1/2}. \quad (1.2)$$

When both sides of equation 1.2 are divided by the d.c. monitor current, I , measured in terms of its value above that needed for monitor cutoff, and when terms are rearranged

$$\frac{I_n}{I} = \frac{(2 v_{eta})^{1/2}}{(I/i)(e/g_a^2)^{1/2}}. \quad (1.3)$$

Now the ratio, I/i , is effectively the amplifier's d.c. gain, g_d . Also the ratio, i/e , is equal to the number of electrons/sec., n , flowing through the diode. Hence

$$\frac{I_n}{I} = \frac{(2 v_{eta})^{1/2}}{[n g_d^2 / g_a^2]^{1/2}}. \quad (1.4)$$

An inspection of the term, $n g_d^2 / g_a^2$, reveals that it represents the number of statistical units per second impressed as a signal on the monitor. Therefore, if \bar{n} is the number of statistical units/mm.²/sec. impressed on the monitor,

$$n g_d^2 / g_a^2 = \bar{n} A / \mu_h \cdot \mu_v, \quad (1.5)$$

where A is the viewing area of the monitor, and μ_h and μ_v are the fractions of the horizontal and vertical scanning times, respectively, during which the beam is in the so-called "on" state. Therefore, when equations 1.4 and 1.5 are solved for \bar{n} ,

$$\bar{n} = \frac{2 \mu_h \cdot \mu_v \cdot v_{eta}}{(I_n/I)^2 \cdot A}. \quad (1.6)$$

Equation 1.6 may be substituted directly in equation 10 of the main text to obtain the values of the system's fluctuation contrast; that is,

$$C_{N\theta} = 2 v_{exc\theta} \cdot (I_n/I) \cdot (A \cdot v_{et\theta} / \mu_h \mu_v v_{eta})^{1/2}. \quad (1.7)$$

Now the contrast, C_o , produced on the television monitor by the sinusoidal signal current, I_s , is by definition

$$C_o = I_s/I. \quad (1.8)$$

Therefore,

$$k = C_o/C_{N\theta} = \frac{(I_s/I) \cdot (\mu_h \cdot \mu_v \cdot v_{eta})^{1/2}}{2 v_{exc\theta} \cdot (A \cdot v_{et\theta})^{1/2}}, \quad (1.9)$$

where $v_{exc\theta}$ and $v_{et\theta}$ are the composite spatial and temporal noise-equivalent-passbands of the visual system, respectively.

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EDITORIALS

ACADEMIC RADIOLOGY

ACADEMIC radiology, as a college discipline, had its beginnings about 150 years after the first two medical schools in Colonial America were founded at the College of Philadelphia in 1765 (University of Pennsylvania) and King's College Medical School in 1768 (Columbia University). The first of these celebrates its 200th anniversary this year. The fact that these schools were established as college affiliations, rather than hospital enterprises, set the academic pattern for teaching the different medical specialties as they developed, and tended to attract students with genuine educational motivation. Academic radiology was no exception, even though much of the earlier teaching was given to postgraduate physicians on a preceptorship basis or in the form of special courses sponsored by scientific organizations and groups with educational interests.

Because of their advanced medical school programs, it is not surprising that academic radiology also had its first formal universities in Philadelphia, New York, Boston, and Baltimore. The names of many famous pioneer radiologists are found on the teaching staffs of these universities. Mostly, they served part-time functions, and since radiology did not enjoy department status at the time, they were members of medical or surgical professorial staffs.

The establishment of academic programs in radiology took place in medical schools throughout the country during the first two decades of the century and coincided with an age of reform in medical education. With the founding of the American Medical Association Council on Medical Education in 1904, followed six years later by the famous Flexner report recommending university affiliation, the number of med-

ical schools dropped from over 160 to 85 by 1920, and the modern era of academic medicine and radiology began. In the next two decades, surviving schools became affiliated with universities, gaining all the benefits and controls associated with this alliance. The full-time system, with various modifications, was gradually accepted by all schools and a closer relationship of the medical school and teaching hospital followed. The first full-fledged endeavor in graduate medical education came when Johns Hopkins University sought to correct the separation of medical school and clinical facilities by constructing the hospital closely adjacent to the basic science divisions. This trend evolved in a further refinement, the medical center, where the medical school, various hospitals, clinics, and public health facilities are established on one geographical site. This medical center concept has since been accepted by all new medical schools and many older schools are converting to it.

Another important factor in the development of medical education has been the growth of postgraduate programs. In the first part of this century, only a small number of graduates elected to take an internship or residency, but the number expanded during the first four decades and has shown rapid growth since World War II, to the point where most postgraduates now take two, three, or more years of training in a specialty, such as radiology.

Academic radiology has grown in size, complexity, and stature during this modern era of medical education, hand in hand with the growth and usefulness of clinical radiology, and influenced by the rapid expansion of medical science itself. The establishment of the American Board of Radi-

ology, in 1934, furthered the aims of academic radiology in promoting higher minimum standards of postgraduate education for certification in the specialty. Several Board members are academic radiologists and many serve as examiners of candidates presenting themselves for certification.

One of the problems of the academician, in recent years, is that what has to be taught has expanded so explosively. It is said that medical knowledge is increasing at the rate of about 9 per cent per year. The schools that formerly turned out a "doctor" in four years have had to retreat from this position and hand the medical student over to a hospital to complete the job. The limits placed by time pose a real problem in medical education. One must teach what is most important as effectively as possible.

The undergraduate radiologic teaching consists chiefly in orientating the student to the "radiologic methods" of diagnosis and treatment, and furnishing some insight into the enormous scientific possibilities of the field. Similar problems exist in the teaching of postgraduate radiology, where the volume of information to be taught calls for additional faculty and physical facilities in order to provide the necessary specialized teaching within the field. Residents no longer receive all their instruction from a teacher of general radiology, but instead are taught different modalities by faculty members who spend their entire time in subspecialties. In addition, after completing his residency, the radiologist now returns to the university for post-postgraduate courses.

Recognizing the need for some identification for the purely academic radiologist,

besieged as he frequently is with problems of how to further high quality investigative research programs and achieve excellence in the pursuit of other academic obligations, a group of young radiology teachers organized an Association of University Radiologists, whose purposes were (1) to increase laboratory and clinical investigation in radiology by the informal exchange of ideas, (2) to stimulate an interest in academic radiology as a medical career, and (3) to advance radiology as a medical science. Members were elected from the radiology faculties of the various medical schools throughout the country, and the First Annual Meeting was held in Chicago in 1952. Today, this organization has a membership of 137 radiologists representing 57 universities. Their two-day annual meeting embraces a program of short reports of scientific works in progress from the various schools and an open Symposium for the exchange of ideas concerning their academic problems. The shortage of qualified academic radiologists remains a challenge to this organization. At this writing, there are at least five departmental chairmanships, and over forty-five faculty positions unfilled in university radiology departments.

Elsewhere in this JOURNAL is a number of papers selected from the program of the 1964 AUR meeting. It is of interest that the development of academic radiology has largely paralleled the life of this JOURNAL, to which it owes much and contributes much.

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RUSSELL J. REYNOLDS

C.B.E., M.B.B.S., F.R.C.P., F.F.R., D.M.R.E.

1880-1964

WITH the death of Dr. Russell Reynolds on November 5, 1964 at the age of 84, radiology loses one of its earliest pioneers and one whose work earned recognition throughout the world.

Russell John Reynolds was born in

London in 1880. At the age of 15, while he was still in school, his father, Dr. John Reynolds, a general practitioner and a friend of Sir William Crookes, read in the newspaper the account of Röntgen's discovery. Such was his interest that, with the

help of his son, an apparatus was constructed in 1896-97. That apparatus was used for research and later for medical practice; it is now on view in the Science Museum at South Kensington. In 1901 Russell Reynolds was elected a member of the Röntgen Society in London and in 1902, while still a student, he demonstrated before the Society an X-ray tube with an adjustable cathode which he had designed. He qualified medically in 1907 and two years later made radiology a full-time occupation.

In the First World War he served in the Royal Army Medical Corps in Britain and in India. Returning to civilian life, he received several hospital appointments, the chief being Physician in Charge of the X-ray Department at Charing Cross Hospital and at the National Hospital, Queen Square. He also became Advisor in Radiology to the Ministry of Pensions and to the Ministry of Supply. In 1932 he was appointed Commander of the Order of the British Empire and in 1938 he was elected Fellow of the Royal College of Physicians. He was appointed Hunterian Professor of the Royal College of Surgeons in 1936, his subject being cineradiography of the oesophagus, stomach and duodenum.

As early as 1921, he began research into the possibilities of cineradiography, a subject which remained his chief interest during the rest of his career. In a room in his house set aside for experiment, and ably assisted by his two sons, both of whom are radiologists, he devised an apparatus in which he incorporated a method of photographing the image thrown onto a fluoroscopic screen. This resulted in a workable cineradiographic unit. The recent introduction of the image intensifier has made cineradiography a recognized part of many examinations, but credit for the pioneer work which led to this belongs to Reynolds.

This has been appreciated and has brought him honors from scientific bodies in many countries. An Honorary Membership in the American Roentgen Ray Society gave him great encouragement. He was also Honorary Member of the New York Roentgen Society, the Canadian Radiological Society, the Society of Radiobiologists of Italy and the Association of Physicians of Vienna, and an Honorary Fellow of the Australian College of Radiology. In 1957 he was presented with the Antoine Bécclère Medal in Paris.

Aware of the importance of the Radiological Societies, he gave them full support; he held office as President of the British Institute of Radiology and of the Radiological Section of the Royal Society of Medicine, and was Warden of the Fellowship of the Faculty of Radiologists.

The above is a brief summary of the achievements of Reynolds' working life, which was full and very worthwhile. Throughout it, he showed foresight and judgment. He was quiet, modest and retiring. Kindness and consideration for all, and especially for those who worked with him as juniors, were endearing features. Anything that he considered important or necessary he would pursue untiringly—an excellent quality when doing research work or building up a department. His appreciation of right and wrong was very definite, and he could be roused easily by anything that he considered slightly unjust.

Russell Reynolds leaves behind him very many friends who will miss him greatly; amongst medical men there is a gap which must result from the loss of such a good colleague who has done such pioneer work.

MONTAGU H. JUPE, F.R.C.S., F.F.R.
Wheatlands Farm
Enborne, Newbury, Berks

NEWS ITEMS

THE AMERICAN COLLEGE OF RADIOLOGY

The Forty-first Annual Meeting of The American College of Radiology was held at the Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, on February 9-13, 1965. The following officers were elected: *President*, Dr. Wallace D. Buchanan, South Bend, Indiana; *Vice-President*, Dr. D. Alan Sampson, Ardmore, Pennsylvania; *Secretary-Treasurer*, Dr. Fay H. Squire, Chicago, Illinois (re-elected). Dr. George Cooper, Jr., Memphis, Tennessee, Dr. Charles G. Stetson, New York, New York, Dr. Seymour F. Ochsner, New Orleans, Louisiana, Dr. Robert W. McConnell, Davenport, Iowa, and Dr. J. Frank Walker, Atlanta, Georgia, were elected to the Board of Chancellors. Dr. Jackson E. Livesay, Flint, Michigan, has taken office as *Chairman, Board of Chancellors*.

The *Executive Director* of the College is William C. Stronach, 20 North Wacker Drive, Chicago, Illinois, and the *Director of Publication Relations* is Otha W. Linton.

The convocation ceremonies were held in the Rose Garden of the Bellevue-Stratford Hotel on February 12, 1965. At these ceremonies Dr. David S. Carroll, Memphis, Tennessee, President of the College, conferred the degree of Fellow on 40 candidates and the degree of Associate Fellow on 2 candidates. The degree of Honorary Fellow was bestowed on Dr. Flemming Norgaard, Copenhagen, Denmark, Dr. Olle Olsson, Lund, Sweden, and *in absentia* on Dr. Paterno S. Chikiamco, Manila, Philippines, Dr. A. N. K. Menon, Madras, India, Dr. Robert McWhirter, Edinburgh, Scotland, Dr. Robert Emil Steiner, London, England, and Dr. Alessandro Vallebona, Genova, Italy.

At the same ceremonies Dr. Carroll, assisted by the new President, Dr. Buchanan, presented Gold Medals of The American College of Radiology "for dis-

tinguished and extraordinary service" to Kenneth Dayton Allison Allen, M.D., Denver, Colorado, Wendell Garrison Scott, M.D., St. Louis, Missouri, and Lauriston Sale Taylor, Ph.D., Bethesda, Maryland.

The Forty-second Annual Meeting of the College will be held at the Drake Hotel, Chicago, Illinois, February 1-5, 1966.

JOSEPH AND SAMUEL FREEDMAN LECTURES

On Saturday and Sunday, April 24 and 25, 1965, Dr. Sidney Nelson, Professor and Chairman, Department of Radiology, Ohio State University, Columbus, Ohio, will deliver the Seventeenth Annual Joseph and Samuel Freedman Lectures in Diagnostic Radiology at the University of Cincinnati College of Medicine. For further details write to Dr. Benjamin Felson, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio 45229.

SPECIAL GRADUATE COURSE IN RADIOLOGICAL PHYSICS

Columbia University offers a one-year course leading to the degree of Master of Science in Radiological Physics; the course is given at the College of Physicians and Surgeons under the auspices of the Radiology Department and the Radiological Research Laboratory. The work is designed to furnish a foundation for those who wish to assist in research and applications of radiological physics, particularly, in radiation protection and dosimetry, and prepares the candidate to carry out the functions of a physicist in a hospital department of radiology. Lectures, seminars, laboratory and clinical work are included. Topics to be considered are elementary and advanced radiological physics, electronics, radiation standardization and protection, radioactive isotopes, biostatistics, radiobiology, instrument design, public health practice, health physics, and clin-

ical applications of radiation physics.

Prerequisite for admission is a bachelor's degree with a major or strong minor in physics, or equivalent scholastic background, and a good academic record. A knowledge of general chemistry and general biology is desirable.

The Division of Radiological Health, Public Health Service, has awarded a grant to the University enabling financial assistance to qualified candidates as part of its national program for the training of radio-

logical health specialists. This aid will be in the form of tuition waiver as well as monthly stipend allowances for full time students. Applicants must be citizens of the United States or have filed a Declaration of Intent. Preference will be given to candidates who are sponsored by public health agencies for work in their area of responsibility or in closely related fields.

Inquiries for further information should be addressed to Dr. W. Gross, 630 W. 168th Street, New York, New York 10032.

ANNOUNCEMENT

This year, beginning with Volume 93, the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY & NUCLEAR MEDICINE has changed from a two volume to a three volume per year publication. This changeover was proposed by the Publication Committee under the Chairmanship of Dr. John F. Roach after consultation with Charles C Thomas and Payne Thomas and was approved by the American Roentgen Ray Society at its Sixty-fifth Annual Meeting held September 29-October 2, 1964 in Minneapolis, Minnesota. The present April issue is the first Index number of the year 1965; the other two will be the August and December numbers, respectively. As before, the JOURNAL will continue to be issued monthly, but in larger size, by Charles C Thomas, Publisher, 301-307 East Lawrence Avenue, Springfield, Illinois, and the annual subscription price remains unchanged.

The AMERICAN JOURNAL of ROENTGENOLOGY, RADIUM THERAPY & NUCLEAR MEDICINE was started as a quarterly publication in 1906 with the designation of "The American Quarterly of Roentgenology." In 1913 it was changed into a monthly publication with one volume per year and one index in December; in 1924, with Volume 11, it was changed to two volumes per year and two indices, one in July and one in December.

The present expansion to three volumes reflects the fruitful result of an ever increasing endeavor to add to the "sum of knowledge." As the frontiers of dynamic radiology continue to widen, the scope of its benefit to mankind broadens by further addition to this sum of knowledge. To quote Lawrence Reynolds, the great Editor of this JOURNAL, "The use of radiant energies—in the future—will be largely an exposition of the thought and effort which we of today contribute toward its advancement."



BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

MAMMOGRAPHY. By Robert L. Egan, M.D., Associate Radiologist, The Methodist Hospital of Indiana, Indianapolis, Ind.; Consultant, Cancer Control Program, Division of Chronic Diseases, Department of Health, Education and Welfare; Consultant, Health Insurance Plan of New York City Mammography Study; Consultant, Glen Cove Community Hospital, Glen Cove, L. I., N. Y.; Formerly, Associate Radiologist, Associate Professor of Radiology, Head of Section of Experimental Diagnostic Radiology, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Pp. 446, with 302 illustrations. Price, \$25.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1964.

Rarely has a book been as timely as this large and excellent volume by Robert L. Egan, who has had so large a role in the recent reawakening of interest in mammography. There is now a widespread demand in many radiologic departments for competent examinations with this method. This clearly written and well illustrated publication will help minimize the disquiet felt by radiologists with limited past experience and will ease the task of self-education that many are undertaking.

This book has large pages and is copiously illustrated with roentgenograms which are well printed and very informative. Presented here are primarily the author's experience and opinions. Both are valuable because his experience is large and his association with clinicians and pathologists has evidently been harmonious and mutually beneficial. Although some of the material has been presented before, the collection into a single source has merit. Full expansion of the author's concepts and liberal illustration of the end results of his technique have resulted in a volume that may well prove to be an enduring masterpiece.

After an introductory chapter reviewing the history of mammography, there are full discussions of the normal breast and the roentgenographic technique. Most of the book is devoted

to two lengthy chapters on malignant and benign breast lesions. In all illustrations the outlines of the breast are rimmed with a black margin which makes the reproductions very effective. Almost 300 roentgenograms are shown, so this is a veritable atlas of mammography.

The book is so good that it is almost a challenge to find minor or personal points over which to quibble. The picture and praise of Stafford Warren are high points in the historic review, yet one cannot help wishing that the magnificent contributions of Gershon-Cohen had received more recognition. Because of the importance of correlating pathologic and radiologic material in mammography, more than 5 of the 433 textual pages might have been devoted to considering pathologic and roentgenographic classification. Likewise, in a method which has a usual error potential of about 10 per cent, there might have been more than 12 pages devoted to text and illustrations about diagnostic difficulties and sources of error.

Compared to the high over-all quality of this book, these suggestions of possible areas for improvement are of minor significance. What is of major importance is that this is a practical, helpful, convincing, well published and thoroughly excellent book.

SEYMOUR F. OCHSNER, M.D.

FUNDAMENTALS OF ROENTGENOLOGY. By Lucy Frank Squire, M.D., Formerly, Clinical Assistant Professor of Radiology, University of Rochester School of Medicine, Rochester, N. Y. Cloth. Pp. 363, with many illustrations. Price, \$12.50. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1964.

The revival of interest in teaching diagnostic radiology to undergraduate medical students can be ascribed to several causes. There is more understanding of the field as a basic part of the clinical armamentarium of the student physician. There is more interest on the part of medical educators in broadening the intellectual horizons of the student. There is a greater ap-

preciation of the vivid tool the roentgen ray represents for the visualization of pathologic anatomy and physiology. As a result, the radiologist is becoming more and more a contributing member of the teaching team. The use of ionizing radiations is becoming less of a mystery and more of an integral part of the student's concept of what comprises the science and art of medicine.

Dr. Squire's book is directed to the concept of instruction in Radiology as a part of the undergraduate medical student's total learning process. It is not a reference work, nor is it a textbook in the traditional sense. It is, rather, an instruction manual, to "... help young physicians learn how to look at X-ray films." The book is planned as a sort of teaching machine. Each page is related to the pages before, and the book includes questions to the reader to enable him to see if he understands the material being presented. The whole volume is directed towards principles of roentgen interpretation and is dedicated to the concept that every graduating physician should "... know how to examine a radiograph and ... be able to derive certain kinds of fundamental information from it."

Dr. Squire has spent many years working on the teaching methods that are evident in this beautifully planned and executed manual. She has succeeded in providing a delightfully clear and interesting introduction to the joys and challenges of our specialty. It is recommended highly as a course book for the student and as a guide for the teacher in introductory courses in diagnostic radiology. We plan to make it the basic text in our course at the Medical College of Virginia.

RICHARD G. LESTER, M.D.

BOOKS RECEIVED

X-RAY EXAMINATION OF THE STOMACH, A DESCRIPTION OF THE ROENTGENOLOGIC ANATOMY, PHYSIOLOGY, AND PATHOLOGY OF THE ESOPHAGUS, STOMACH, AND DUODENUM. Revised edition. By Frederic E. Templeton, M.D., Clinical Professor of Radiology, The University of Washington, Seattle, Wash. Cloth. Pp. 598, with many illustrations. Price, \$15.00. University of Chicago Press, Chicago, Ill., 1964.

FUNDAMENTALS OF ORTHOPAEDICS. By John J. Gartland, A.B., M.D., Assistant Professor of Orthopaedic Surgery, Jefferson Medical College, Philadelphia, Pa. Cloth. Pp. 338, with many illustrations. Price, \$8.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa., 1965.

THE SCIENCE OF IONIZING RADIATION: MODES OF APPLICATION. Edited by Lewis E. Etter, B.S., M.D., F.A.C.R., Professor of Radiology, Western Psychiatric Institute and Clinic and the Falk Clinic, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.; Consultant, C. Howard Marcy State Hospital, Pittsburgh, Pa. Cloth. Pp. 788, with many illustrations. Price, \$26.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1965.

SPINAL CORD DISEASES: A RADIOLOGIC AND MYOLOGRAPHIC ANALYSIS. By Guido Lombardi, M.D., Chief Radiologist, Istituto Neurologico di Milano; and Angelo Passerini, M.D., Senior Assistant Radiologist, Istituto Neurologico di Milano, Milan, Italy. Cloth. Pp. 175, with many illustrations. Price, \$8.50. The Williams & Wilkins Company, Baltimore 2, Md., 1964.

MATHEMATICS FOR RADIOGRAPHERS. Second edition. By L. A. W. Kemp, B.Sc., Ph.D., F.Inst.P., Physicist to the London Hospital; Formerly, Lecturer in Physics at The Polytechnic, London, England. Cloth. Pp. 220, with 87 illustrations. Price, \$6.00. F. A. Davis Company, 1914-16 Cherry Street, Philadelphia, Pa., 1965.

RÖNTGENBEFUNDE AM KINDLICHEN BECKEN BEI ANGEBORENEN SKELETTAFFEKTIONEN UND CHROMOSOMALEN ABERRATIONEN. By Priv.-Doz. Dr. Herbert J. Kaufmann, Leiter des Röntgeninstituts am Basler Kinderspital, Kinderklinik der Universität Basel. Cloth. Pp. 86, with 82 illustrations. Price, DM 44,-. Georg Thieme Verlag, Stuttgart, Germany. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N.Y., 1964.

SAMSON WRIGHT'S APPLIED PHYSIOLOGY. Eleventh edition. Revised by Cyril A. Keele, Professor of Pharmacology and Therapeutics, University of London, at The Middlesex Hospital Medical School; and Eric Neil, John Astor Professor of Physiology, University of London, at The Middlesex Hospital Medical School. With the collaboration of John B. Jepson. Cloth and Paper. Pp. 534, with 387 illustrations. Price, Cloth, \$14.00, Paper, \$9.50. Oxford University Press, Inc., 417 Fifth Avenue, New York, N.Y., 1965.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

GENITOURINARY SYSTEM

SCHOLZ, A., HAUGE, A., and OEFF, K. Isotope renography in the diagnosis of renal hypertension. *German Med. Monthly*, July, 1964, 9, 269-275. (Address: Nuklear-Medizinische Abteilung der Medizinischen Universitätsklinik, Städt. Krankenhaus Westend, Spandauer Damm 130, Berlin-Charlottenburg 9, Germany.)

Isotope renography is of value in the differential diagnosis of hypertension due to unilateral renal disease.

A total of 43 hypertensive patients was investigated. The criteria used were based on: history, clinical examination, ophthalmoscopy, urine tests, blood urea, test of concentrating power, intravenous pyelography with retrograde pyelography performed in a few cases, radioisotope renography, inulin and PAH clearances at a constant plasma level, and renal arteriography.

Ten of 11 patients with unilateral renal artery disease had an abnormal radioisotope renogram. In a case of complete renal artery occlusion the curve was that of a nonfunctioning kidney: after the initial rise in the vascular phase, the further rise expected in the secretion phase failed to occur and the curve turned downward immediately. In cases of incomplete renal artery obstruction the peak of the secretion phase was delayed on the side of the stenosis in 9 out of 10 cases. The delay ranged from 45 seconds to 6 minutes. In only 3 cases was there an abnormality in the rise of the vascular phase.

In cases of unilateral chronic pyelonephritis or unilateral contracted kidney there are clear-cut changes in the radiorenogram. In advanced cases with steadily worsening renal function the rise in the secretion phase becomes less and less until in the last stages of unilateral contracted kidney the picture is that of total or almost total nonfunction. The diseased kidney may not show a secretion maximum at all. If there is one, it will be reached considerably later than the peak on the healthy side.

In hypertensive patients with bilateral renal disease the radiorenograms in both kidneys usually show a smaller rise in the secretion phase than is seen in normal controls. The renogram in these cases, however, may be normal. In cases with hypertension without renal involvement the renograms were normal.

Previous investigators have devoted most of their attention to the vascular phase in assessing renography for evidence of renal artery stenosis. Three of 9 patients with renal artery stenosis in this series showed no diminution of the rise in the vascular phase. This is because this phase is determined to an extent of over 50 per cent by blood in the large vessels and around the kidney. Secretory function in the

kidney makes a further contribution to the rise. Therefore, any reduction in the renal blood flow has to be very large before it becomes apparent. The important finding in these cases is the delay in reaching the peak of the curve. This, however, is seen in many other conditions including pyelonephritis and forms of obstruction to urinary outflow. This implies that the diagnosis of unilateral renal artery stenosis cannot be made from the renogram alone.—*David Morse, M.D.*

NERVOUS SYSTEM

SOLÉ-LLENAS, J. Mielografía gaseosa. (Gas myelography.) *An. med.*, Barcelona, 1963, No. 4, 58-67. (From: Clínica Médica A de la Facultad de Medicina de la Universidad de Barcelona, Spain.)

The history of gas myelography is reviewed briefly.

Gas myelography may be carried out with oxygen or air and may be total or partial, the latter including localized studies of the cervical or lumbar region.

In general, the technique introduced by Lindgren (*Acta chir. scandinav.*, 1939, 29, 303) is followed, in which the patient is placed in the 25 degree Trendelenburg position; then 10 ml. spinal fluid is removed and 10 ml. of gas injected by increments until the spinal pressure reaches 250-300 mm. of water. The spinal cord and subarachnoid space may be visualized with the additional aid of tomography. Roth (*Acta radiol.*, 1963, 1, 53) also reported a method of gas myelography utilizing lumbar puncture, whereas the method of Lindgren utilizes cisternal puncture. Jiroud (*Acta radiol.*, 1958, 50, 221) described a method of cervical gas myelography utilizing lumbar puncture. Plain roentgenograms may suffice for study of the cervical region.

Intramedullary tumors show expansion of the cord; intradural tumors may show a filling defect and displacement of the cord. The arachnoid adhesions appear as irregular shadows. Degenerative disk disease in the cervical region as well as various forms of block may also be demonstrated.

The air is usually absorbed within 24 to 48 hours and, although there may be headache or backache up to 48 hours, there is less inconvenience than is encountered following the use of iodized oils.—*Charles M. Nice, Jr., M.D., Ph.D.*

HERNÁNDEZ-ROS, A. (Madrid, Spain.) Discografía: exploración discográfica de la columna lumbar. (Diskography; diskographic exploration of lumbar spine.) *An. med.*, Barcelona, 1963, No. 4, 67-93.

Some perforations of the annulus fibrosus and certain forms of degenerative disk disease do not show deformity on myelography. In such instances diskography may be of significant value.

The guide needle is inserted about 4-5 cm. from the midline and directed toward the intervertebral

disk. A slender needle is then introduced through the larger needle and directed toward the middle of the disk. Water soluble contrast material is used. The fourth and fifth lumbar disks are the most usual locations of pathology but the second and third lumbar disks are sometimes also injected.

Diskography definitely helps to determine if the disk is normal. Fissures and degenerative changes are very well shown. Beginning herniation and actual rupture of the annulus may be demonstrated. The reproduction of clinical pain patterns upon injection is likewise of diagnostic importance.—*Charles M. Nice, Jr. M.D., Ph.D.*

SKELETAL SYSTEM

VENABLE, JOHN R., FLAKE, RAYMOND E., and KILIAN, DUANE J. Stress fracture of the spinous process. *J.A.M.A.*, Dec. 7, 1964, 190, 881-885. (Address: Dr. Venable, Dow Chemical Co. B-111 Park Road, Freeport, Texas.)

Twenty-eight fractures of the spinous processes of the lower cervical and upper thoracic vertebrae were seen in 24 patients who worked as metal dippers, an occupation which places repetitive stress on these areas.

The case histories are similar: the worker feels a snap between the scapulae; moderate interscapular pain, which is relieved by rest, usually follows. Physical examination shows the head flexed slightly with exaggeration of the kyphotic curve and elevation of the shoulders. Motion of the upper spine, arms, and head is limited. Palpation of the interscapular area reveals muscle spasm and tenderness. There is local tenderness over the spinous process of C7 or T1; crepitation over these two areas is clinically significant.

Roentgenographic examination provides a definitive diagnosis. On the anteroposterior roentgenogram a double shadow is caused by the caudad displacement of the avulsed fragment and is regarded as evidence of a fracture. Lateral or oblique views should always be obtained, and although soft-tissue thickness may present difficulties, the diagnostic accuracy increases with improved roentgen techniques.

Ten patients had surgical removal of the avulsed fragment; 14 were treated conservatively.—*Lois Cowan Collins, M.D.*

ROTH, SANFORD I. Squamous cysts involving the skull and distal phalanges. *J. Bone & Joint Surg.*, Oct., 1964, 46A, 1442-1450. (From: James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston 14, Mass.)

The author reviewed the clinicopathologic aspects of 10 patients with squamous cysts of the phalanges and 11 patients with squamous inclusions of the

skull. The mean age of patients with phalangeal lesions was 42 years, compared with a mean age of 18 years for those with squamous cysts of the skull.

Three cases were unique: one was the first recorded case of squamous cysts in the distal phalanges of two different fingers in the same patient; the second was the first recorded case of squamous cyst of the distal phalanx of a toe; and the third, the youngest reported patient (2 months old) with a squamous cyst of the skull.

The most common symptom of patients with a skull lesion was a mass, showing nonsclerotic margins and involving one or both tables. Pain was the most common complaint of those with phalangeal lesions, which roentgenographically revealed irregular, lytic, medullary defects that had expanded, thinned, or broken the cortex, usually on the dorsal surface.

Most authors suggest that phalangeal cysts are of traumatic origin, resulting from displacement of epidermis into the dermis. On the other hand, most authors have concluded that squamous cysts of the skull were of nontraumatic origin.

Adequate therapy consists in removal of the cyst and its wall by curettage or removal of the involved portion of bone.—*Francis P. Shea, M.D.*

WETZEL, H. Progressive diaphyseal hyperostosis (Camurati-Engelmann's disease). *German Med. Monthly*, July, 1964, 9, 285-287. (Address: Medizinische Klinik des Städtischen Krankenhauses, Ludwigshafen/Rhein, Germany.)

Progressive diaphyseal hyperostosis (Camurati-Engelmann's disease) is a hereditary disorder involving certain bony structures. It may develop at any age. The youngest patient reported was 3 months and the oldest 55 years old. A clumsy, rolling "sailor's gait," abnormally long extremities and hypoplastic muscles with easy fatigability are characteristic signs. Bone and muscle pain, mental retardation, thickening of the mandibles, craniomegaly and deafness have been reported. Facial paralysis and deafness were dominant features of the 2 cases reported. Both were due to mechanical pressure resulting from hyperostosis of the skull.

The laboratory findings are usually normal.

The 2 cases reported exhibited characteristic changes roentgenologically. There was marked sclerosing hyperostosis of the base of the skull, especially the anterior and middle cranial fossae but to a lesser extent the occipital bone and mandible were involved. The petrous bones were markedly involved.

Definite hyperostosis was found in the diaphyseal region of the femurs decreasing toward the metaphyses. The epiphyses were normal. Symmetric, severe thickening of the compacta and cortex was present in all long bones. The diaphyses were spindle shaped and the marrow space narrowed. The outer contour was undulating and of varying contour.

Life expectancy is not affected by this disorder.—
David Morse, M.D.

EYRING, EDWARD J., PETERSON, C. A., and BJORNSON, D. R. Intervertebral-disc calcification in childhood: a distinct clinical syndrome. *J. Bone & Joint Surg.*, Oct., 1964, 46A, 1432-1441. (Address: Dr. Eyring, Department of Orthopaedic Surgery, University of California Medical Center, San Francisco 22, Calif.)

Intervertebral disk calcification in children, although occasionally asymptomatic, is usually associated with a rather typical set of clinical findings which include pain, limitation of motion, local tenderness, and evidence of inflammation characterized by temperature elevation, and increased sedimentation rate or white blood cell count. Moreover, the involved disks may prolapse in any direction. A conservative therapeutic regimen is sufficient unless there is evidence of prolapse into the spinal canal.

A series of cases is presented which, together with that of Newton, represents the only large series of disk calcifications with associated symptoms in which children have been followed for prolonged periods. Residual deformity of the spine in children followed for as long as 13 years was observed, as well as failure of complete resorption of calcium.

The following factors appear to constitute the syndrome of intervertebral disk calcification: (1) pain, local or referred; (2) limitation of spine motion; (3) evidence of inflammation; (4) intervertebral disk calcification; (5) pediatric age group only; and (6) self limited clinical course.

Among the cases reviewed, there were 31 boys and 16 girls. The average age was approximately 7 years. Usually, calcium was discovered from 1 to 60 days after the onset of symptoms.

The authors suggest that trauma of varying degree, coupled with degenerative changes, sets the stage for deposition of calcium. Inflammatory reaction accompanies this calcification and results in pain.—*Francis P. Shea, M.D.*

BLOOD AND LYMPH SYSTEM

GROLLMAN, J. H., JR., and HANAFEE, WILLIAM.

The roentgen diagnosis of Takayasu's arteritis. *Radiology*, Sept., 1963, 83, 387-395. (From: Department of Radiology, University of California, Center for the Health Sciences, Los Angeles, Calif. 90024.)

Takayasu's arteritis, a disease found most commonly in young adults, with females predominating, involves chiefly the aortic arch and its proximal branches although changes occasionally have been reported in other vessels. The exact etiology is unknown, but the condition is generally classed among the diseases of autoimmunity. It is chronic, progres-

sive, and inflammatory, characterized by a panarteritis leading to fibrosis and resultant obliteration of the vessel lumen. Symptomatically, complaints are referable to the brain, eyes, and upper extremities secondary to ischemia in these areas. The clinical aspects vary depending on the location and degree of narrowing of the vessel lumen. The condition is classed as a subdivision of the aortic arch syndrome in which the main finding is obliteration of the brachiocephalic pulses. It must be differentiated from the more common arteriosclerosis and syphilitic aortitis, and the less common causes of the aortic arch syndrome such as arterial embolism and thrombosis, dissecting aneurysm, the thoracic-outlet syndrome, congenital coarctation, pseudoxanthoma elasticum, thromboangiitis obliterans, polyarteritis nodosa, and trauma.

The diagnosis is made by the clinical history and the roentgenographic findings demonstrated by aortography. Arteriography is important to determine the degree and extent of involvement so that the proper surgical procedures can be decided upon. The characteristic arteriographic changes found are: (a) the localization of the process to large arteries near their origin, particularly the brachiocephalic trunk, with sparing of the vessels distally; (b) localized smooth constrictions and flame-shaped occlusions; (c) the presence of a well developed collateral circulation.

Six case reports are presented by the authors and the roentgenographic findings in these cases are illustrated. Their present technique of aortography, a modified Seldinger approach, is briefly described.—*Donald N. Dysart, M.D.*

WERTHEIMER, P., FROMENT, R., DES COTES, J., SITE, J., and WEBER, B. (Lyon and Colmar, France.) Exiguïté artérielle constitutionnelle: facteur probable de thrombo-artériose du type Buerger. (Constitutional narrowing of the arterial vessels: a probable factor in Buerger's type of thrombo-arteriosclerosis.) *Presse méd.*, Sept., 1964, 72, 2259-2264.

As a result of the work of Leo Buerger, a specific type of arterial disease has been described which commonly carries his name. The etiology of this disease is not known. It is characterized by a chronic arteriopathy in a younger age group as compared with arteriosclerosis. It is completely independent of the latter, which affects the older age group. The term thrombo-arteriosclerosis is suggested instead of thrombo-angiitis.

The striking findings obtained during arteriography are: the slender or reduced caliber of an entire artery; clearly defined vessel wall which is smooth, regular and rigid, presenting the appearance of a stretched cord. Arterioles are relatively few, which are likewise slender, fine and small. The caliber remains unaltered under general anesthesia as well as

following the intra-arterial injection of novocaine, prior to arteriography. Thus spasm is ruled out as a cause of the narrowness of the vessels.

The authors' series includes 148 patients studied by means of angiography. Of these, 36 were normal, 30 had thrombo-angiosis and 82 had atheromatous arterial disease.

Careful measurements, with increased target film distance (at least 1.5 meter), obviated the factor of roentgenographic distortion.

The authors found that there is an average decrease of caliber of 20 per cent in thrombo-angiosis (Buerger's disease) as compared with the diameter of the normal vessel or the diameter of an atheromatous vessel, with a margin of error of not more than 1 per cent. On the other hand, the diameter of the normal vessel and that of the arteriosclerotic or atheromatous vessel was essentially the same.

Arterial measurements were made on the aorta at the level of the fourth lumbar vertebra.

Based on their studies, the authors conclude that Buerger's disease is a constitutional disorder, probably familial, occurring in patients relatively younger than those with atheromatous arterial disease.—*William H. Shehadi, M.D.*

SCHONHOLTZ, GEORGE J., and JAHNKE, EDWARD J., JR. Occult injury of the thoracic aorta associated with orthopaedic trauma. *J. Bone & Joint Surg.*, Oct., 1964, 46A, 1421-1431. (Address: Dr. Schonholtz, 730 24th Street, N.W., Washington 37, D.C.)

The thoracic aorta may rupture after nonpenetrating trauma. A significant number of cases survives for varying periods, allowing surgical repair if the proper diagnosis is made. Musculoskeletal injuries are often predominant in the early clinical picture. Case reports of 5 new cases of occult injury of the thoracic aorta are presented.

Of all types of thoracic aneurysms, the traumatic variety appears to account for approximately 2 to 6 per cent. The cause is usually rapid linear deceleration secondary to an automobile or motorcycle accident. Aortic ruptures generally occur at the isthmus just distal to the left subclavian artery. The initial tear of the aortic wall is usually circumferential and varies in extent from mild intimal damage through intimal and medial laceration of varying size to complete transections. The tear may be temporarily sealed off, but the thrombus may disintegrate and the patient exsanguinate at any time during the first 4 weeks after injury. Survival ultimately depends on the formation of a mediastinal hematoma or containment of hemorrhage by the adventitial coat of the aorta. Following this early period, the lesion matures into an aneurysm which may rupture months or even years later.

Thus, the most constant and helpful diagnostic roentgen finding is widening of the superior mediasti-

num. Aortography may be employed to confirm the diagnosis.

Once the diagnosis is made, especially during the first 30 days following injury, immediate thoracotomy is indicated. The preferred surgical procedure is excision of the damaged segment and replacement with a teflon graft.—*Francis P. Shea, M.D.*

JUDKINS, MELVIN P., and DOTTER, CHARLES T.

An uncommon complication of thoracic aortography: a case report. *Radiology*, Sept., 1964, 83, 433-435. (From: University of Oregon's Minthorn Memorial Laboratory for Cardiovascular Research through Radiology, Portland, Ore.)

A single case is reported in which catheter trauma apparently led to atheromatous embolization of the middle cerebral artery (autopsy) and thereby to death of a 60 year old patient undergoing attempted retrograde aortography. It is emphasized that cerebral signs and symptoms developed just prior to the contemplated injection of contrast medium, that none was injected, and that therefore the death cannot be attributed to contrast agent toxicity. The authors thus take exception to a report of a somewhat similar case where death was ascribed to a serious immediate reaction to the contrast medium, but where an autopsy was not performed.

At the Minthorn Memorial Laboratory for Cardiovascular Research through Radiology, Portland, Oregon, the recognized incidence of this complication is roughly 1 in 1,000. However, reference is made to reports suggesting that microemboli may occur more frequently but do not lead to clinically detectable consequences.

One photomicrograph shows a section of the right middle cerebral artery occluded by a typical atheroma.—*Glenn W. Pett, M.D.*

GENERAL

MORETTI, EDOARDO. Sur la calcinose généralisée. (On generalized calcinosis.) *J. de radiol., d'électrol. et de méd. nucléaire*, Aug.-Sept., 1964, 45, 433-438. (From: Institut de Radiologie de l'Hôpital de Busto Arsizio, Italy.)

The author states that calcifications may be classed as (1) metastatic, (2) dystrophic, and (3) those occurring in calcinosis, which may be either local or generalized.

Calcinosis has no typical roentgenologic picture because of the polymorphism of the calcific formations and their varied evolutive cause. In the diffuse or generalized form the prognosis is severe: the deposits are extensive, affecting not only the skin and subcutaneous tissues, but tendons, nerves, muscles, fascia, joints and periarticular structures. The disease is rare, only 200 cases having been recorded. Clini-

cally the onset is often in the first decades of life and evoked by rheumatoid disease, or peripheral circulatory lesions, as in Raynaud's disease; it may be associated with collagen diseases such as scleroderma or dermatomyositis. Apparently this is a chronic inflammatory condition in which there is a special tissue affinity for calcium salts.

The author's case, a male, age 31, had his original symptoms at age 10. Over the years inflammatory tumefactions would appear, often ulcerating and exuding milky fluid. The end result was massive calcifications involving deep structures which produced immobility and complete disability. Studies of renal and cardiac function, and of calcium and phosphorus metabolism failed to reveal abnormalities. There was a marked hypergammaglobulinemia.

Eight roentgenographic reproductions are presented which delineate massive calcific masses in muscles, about the knees, shoulders, axillae and in other deep tissues.—*Frank A. Riebel, M.D.*

HUNG, WELLINGTON, JARMAN, W. DABNEY, WIGGER, H. JOACHIM, and JACOBSON, CECIL. Turner's syndrome in a 6-year-old Negro boy. *J. Urol.*, Oct., 1964, 92, 317-322. (From: Departments of Endocrinology, Urology and Pathology, Children's Hospital of District of Columbia, and Departments of Pediatrics and Urology, George Washington University, Washington, D. C.)

Turner's syndrome is characterized by a sexual infantilism, congenital defects of the skin and appendages, and anomalies of the cardiovascular and skeletal systems. In females, it is usually associated with chromosomal abnormalities and lack of ovarian tissue.

In this article, the abnormal syndrome is reported in a 6 year old male child. In addition to multiple congenital anomalies, this child had undescended testicles. Testicular biopsy showed a decrease or absence of spermatogonia in the tubular epithelium.

The authors briefly review in tabular form 11 other cases of similar nature from the literature. All roentgenologic examinations carried out on the patient included in this report were normal.—*George W. Chamberlin, M.D.*

FAINSILBER, B. T., and GOSSELIN, J. (Paris, France.) Variante de la triade de Saint. (A variant of Saint's triad.) *J. de radiol., d'électriol. et de méd. nucléaire*, Aug.-Sept., 1964, 45, 463-464.

The classic Saint's triad consists of association of hiatus hernia, cholelithiasis and colonic diverticula, to which some authors add uterine cancer.

In the reported case there are variants in two of the signs: the gallbladder was of the calcified or porcelain type, there was a Meckel's diverticulum without

colonic diverticula, and there was cancer of the breast.—*Frank A. Riebel, M.D.*

RADIATION THERAPY

ADAMS, GAIL D. The use of a 70-mev. synchrotron in cancer therapy. I. Physical aspects. *Radiology*, Nov., 1964, 83, 785-796. (From: Radiological Laboratory, University of California San Francisco Medical Center, San Francisco, Calif. 94122.)

A 70 mev. synchrotron, designed by Pollack and built by the General Electric Company, was used to treat cancer. This medical synchrotron is comprised of four major components: magnet unit, capacitor bank, operative circuitry, and means for controlling angulation and altitude of the magnet unit. The electrical circuits are the usual for this type synchrotron, and the main power consumption of about 40 kw. is used in energizing the magnetic field. A preventative maintenance schedule was adopted, and only two days of treatment time were lost since 1956 due to machine malfunction.

The roentgen-ray beam is produced by electrons striking a platinum target which protrudes into the donut. The field contour is determined by a lead alloy collimator 24 cm. thick. A compensator is used to produce field flattening. Dose calibration and standardization was done with a circular field at TSD $+10=200$ cm. Other distances and fields were done using the inverse square law with a modification factor. The conventional ferrous sulfate dosimeter system was chosen as the laboratory standard, with another chemical dosimeter system used for daily work. Measuring the quantity of radiation exposure was first done by measuring induced activity in a foil, but later a transmission ionization chamber (placed between the quadrant chamber and collimator) was used, integrating the charge conducted during each exposure. Typical absorbed dose with TSD of 190 cm., measured at 200 cm., was 60 rads per minute. Depth dose is at a maximum from about 8 to 11 cm. Exit doses may approximate 80 per cent. Some photo-neutrons are produced with the roentgen rays, but appear to be about 0.1 per cent of the roentgen-ray dose. Most treatment was done using one or two fields. Several typical isodose curves are shown as used in treatment planning.—*James C. Moore, M.D.*

STONE, ROBERT S., and LOUIE, ROSE V. The use of a 70-mev. synchrotron in cancer therapy. II. Clinical aspects. *Radiology*, Nov., 1964, 83, 797-806. (From: Radiological Laboratory, University of California Medical Center, San Francisco, Calif. 94122.)

In 1951 a 70 mev. synchrotron was installed, and in 1956 clinical trials were started using the machine. Many problems had to be solved, and one of the first

was determination of the RBE of the 70 mev. roentgen rays. This was done using yeast, with a 250 kv. machine as a standard, and was found to be between 0.86 and 0.88. This RBE was found to be correct clinically. Average dose per minute was 50 rads per treatment; 1,000 rads per week; total dose in 6 to 8 weeks was 6,000 rads or more.

Field localization was done in the usual manner, and treatment planning was carried out keeping in mind the characteristics of the roentgen-ray beam. The isodose curves show that the region from 6 to 14 cm. received 95 per cent or more of the maximum absorbed dose. The entry port received practically no dose, while the exit dose might be 80 per cent. Combining anterior and posterior ports accomplished more uniform irradiation of thicker body parts. Bolus was used to bring the depth dose nearer the surface. Another advantage of the machine was the extreme flatness of the absorption curve at 6 to 14 cm. depth; this allowed more uniform irradiation of all parts of the tumor. Usually only one or two fields were used for treatment, which made treatment planning relatively simple.

Initially only patients with advanced lesions were accepted for therapy, and consequently a high cure rate was not expected. As more patients were treated it became obvious that the greatest usefulness of the 70 mev. beam of roentgen rays was in the therapy of cancer in the thick regions of the body, especially of obese patients. An effort was then made to concentrate on tumors of the urinary bladder and the uterus. Experience treating tumors in these two organs is reported: 83 cases of cancer of the urinary bladder and 72 cases of cancer of the uterus. In cancer of the bladder, in the limited follow-ups available, local tumor was eradicated in 41 per cent. Preliminary studies indicate that treatment of uterine cancer was satisfactory or superior to other methods.

The integral dose with 70 mev. roentgen-ray therapy is lower than with lower energy beams, and fewer systemic reactions occur. However, it is not possible to treat tumor without giving the immediately adjacent tissues nearly the same dose. Thus 70 mev. roentgen rays have the same effect as other radiations having the same absorbed dose. In carcinoma of the bladder (83 patients) 12 had complications, with rectal or sigmoid stricture and fistula being the most common. Eleven of 72 patients treated for uterine carcinoma had complications, with fistula involving the intestines being the most common. These uterine carcinoma patients were treated with fractionation over a period of 6 weeks or longer, and no faster than 1,000 rads per week. Systemic reactions were mild and in keeping with the lowered integral dose.

While it has not yet been demonstrated that any greater curative or palliative effects are to be obtained, the 70 mev. beam of roentgen rays is useful, especially for treating deepseated cancer.—*J. C. Moore, M.D.*

McGUFF, PAUL E., DETERLING, RALPH A., JR., GOTTLIEB, LEONARD S., FAHIMI, H. DARIUSH, BUSHNELL, DAVID, and ROEBER, FRED. The laser treatment of experimental malignant tumours. *Canad. M. A. J.*, Nov. 21, 1964, 91, 1089-1095. (From: Department of Surgery, Tufts-New England Medical Center; Mallory Institute of Pathology, Boston City Hospital; and Advanced Development Laboratory of the Raytheon Co., Wayland, Mass.)

The laser, an intense beam of energy in the form of photons of light, has been developed in the last 4 years. This light has the unique characteristics of being coherent, monochromatic and capable of high intensity.

The authors used this intense light energy to treat 20 different types of malignant tumors, experimentally implanted in the cheek pouches of Syrian hamsters during the past 2 years. One half of the hamsters were subjected to laser energy and the other one-half were kept as controls.

Superficial melanotic and amelanotic malignant melanomas responded favorably. In implants of thyroid carcinoma of human origin likewise gratifying results were obtained.

The thermal decay time, the time required for a tumor to return to normal temperature after reaching a maximal temperature, was found to be 6 to 12 times greater for tumors treated with laser energy than for tumors treated with cautery. The pattern of healing was also found to be completely different. The effect of laser energy on normal tissue was minimal and healing was rapid while in certain types of malignant tumors it has been found to produce regression or complete dissolution. This was explained by the theory that the laser energy may inactivate or change the specificity of an enzyme essential to the tumor's metabolism.

The authors discuss their experience with laser therapy in 4 human patients. Complete and total dissolution of the tumor tissue was lacking in some of these cases, indicating that higher energies may be required than were used in the animal experiments. The point is made that it is likely that a more profound biologic effect may be obtained with a laser of lower wave length than that provided by ruby.

Sixteen photographs and a conceptual drawing are included in this article.—*Kenneth M. Nowicki, M.D.*

CHAVANNE, G., CALLE, R., and GATTO, I. Le cancer mammaire "bilatéral d'emblée," découverte de la deuxième localisation par la mammographie bilatérale systématique. (Concurrent bilateral breast carcinoma; discovery of the second localization by systematic bilateral mammography.) *J. deradiol., d'électrol. et de méd. nucléaire*, Aug.-Sept.,

1964, 45, 447-450. (From: Fondation Curie, Paris, France.)

The authors believe that any roentgenologic investigation of the breast must obligatorily be bilateral, since this may allow the discovery of a second carcinoma on the opposite side.

Among 2,000 patients with carcinoma of the breast so studied at the Curie Foundation, 19 were discovered to have provable malignancies on the contralateral side. This 1 per cent incidence is consistent with reports by other observers; actually, however, the true incidence is closer to 2 per cent, since some tumors are missed and others are excluded from the series for lack of histologic proof.

Roentgenologically the lesions may have a smooth contour, may have a stellate nodular appearance, or exhibit micro-calcifications without visible tumor. With proper technique one can hope to identify lesions down to 5 or 6 mm.—*Frank A. Riebel, M.D.*

RADIOISOTOPES

ROSENTHALL, LEONARD. A fifteen minute test of the rate of thyroid trapping of radioiodine. *J. Nuclear Med.*, Sept., 1964, 5, 657-663. (From: Department of Radiology, Montreal General Hospital, Montreal, Quebec, Canada.)

Previous studies of the early uptake of I^{131} by the thyroid gland used the percentage of the administered dose accumulated in the gland at a certain time as an index of functional capacity. The present study used continuous counts made over the thyroid gland on a strip chart recorder after the intravenous injection of about 20 μ c of I^{131} . The ratio of the net counts at 15 minutes to that at 5 minutes was determined and the ratio was called the trapping index (R_{15}). The R_{15} is a relative rather than an absolute measurement and is independent of the administered dose.

The upper euthyroid limit of R_{15} was found to be 1.34. The lower hyperthyroid limit of R_{15} was 1.24. Approximately 95 per cent of the euthyroid cases were between an R_{15} of 1 and 1.3; 83 per cent of the cases with an R_{15} of less than 1 were hypothyroid. In the 35 hypothyroid cases studied, 71 per cent had an R_{15} of less than 1.

The relationship of R_{15} to the T_{24} uptake is: $\log R_{15} = 0.292 \log T_{24} - 0.334$. The coefficient of correlation is 0.87 if the R_{15} is not less than 1.

The trapping index (R_{15}), the 24-hour uptake (T_{24}) and the clinical state were compared in 310 patients. The R_{15} was superior to the T_{24} uptake in separating hyperthyroidism from euthyroidism. Nine per cent of the hyperthyroid cases were within normal limits with R_{15} , as compared with 38 per cent for T_{24} . The T_{24} was slightly better in distinguishing euthyroidism from hypothyroidism.

The effects of TSH stimulation and T_3 suppression can be determined within 15 minutes using the R_{15}

test. The R_{15} test can be quite helpful in studying the pathophysiology of thyroid disorders, such as iodine induced goiters, large nontoxic goiters and toxic adenomas.

A partial extravasation of the injected I^{131} is the major source of error in the R_{15} test. The R_{15} is relatively insensitive to small changes in the crystal-skin distance. I^{131} can be used instead of I^{125} if the T_{24} uptake study is not needed and the thyroid would receive about 1/30 the amount of irradiation.—*Charles W. Cooley, M.D.*

KEIDERLING, W., EMRICH, D., HAUSWALDT, CH., and HOFFMANN, G. The use of radio-iodine in the reduction of euthyroid goitres. *German Med. Monthly*, July, 1964, 9, 265-269. (Address: Medizinische Universitätsklinik, Hugstetterstr. 55, Freiburg i. Br., Germany.)

According to Bergfeld 50 per cent of the urban population and 75 to 100 per cent of the rural population of Southern Baden have endemic goiters. Whereas in Switzerland the compulsory addition of iodine to food salt provides goiter prophylaxis, such measures are lacking in Western Germany.

A total of 379 patients with euthyroid goiter was treated by radioactive iodine from 1952 to April 1963.

The following were considered indications for attempting to reduce the size of the thyroid by radioiodine therapy: (1) Marked subjective mechanical complaints. The most prominent complaint was dyspnea on exertion or lying down; (2) objectively demonstrable mechanical pressure manifestations such as radiologic evidence of narrowing or displacement of the trachea, stridor or venous congestion in the neck; and (3) inadvisable operation because of associated disorders or refusal by the patient for personal reasons.

The fulfilment of the following criteria was required before I^{131} therapy was undertaken: (1) the estimated weight of the gland should exceed 50 grams; (2) minimum age of the patients should be 35 years; (3) the patient must be euthyroid both clinically and in the two phase radioiodine test; (4) the maximum radioiodine uptake by the thyroid should be 45 per cent or more of the tracer dose; and (5) the scintigram taken during the radioiodine test should show a homogeneous distribution of the tracer dose throughout the thyroid gland. Patients with "cold nodules" were usually submitted to surgery and only treated with radioiodine in exceptional circumstances.

The dose was 15,000 to 18,000 rads per gram of thyroid gland. The treatment was repeated in 3 to 4 months if inadequate results were obtained after the first treatment. Three-fourths of the patients required on the average a single dose of up to 20 mc I^{131} . The total dose did not exceed 40 mc in 85 per cent of patients.

Patients with marked narrowing of the trachea were given prophylactic prednisone to prevent further narrowing of the trachea which might result from radiation thyroiditis.

Objective improvement was estimated by decrease in gland size, neck circumference and pressure manifestations which occurred in two-thirds of all patients.

The incidence of side effects was low. Five per cent of patients developed mild radiation thyroiditis which usually subsided spontaneously. Two patients required tracheotomy following development of acute dyspnea. Clinical manifestations of hypothyroidism were observed in 1.6 per cent.

The more serious the pressure manifestations were before therapy, the greater was the likelihood of a favorable result.

Radioiodine therapy would thus appear to be the method of choice for the treatment of recurrent goiter and in patients over 30 years of age with goiters which are either inoperable or entail an increased operative risk.—*David Morse, M.D.*

HAYNIE, THOMAS P., OTTE, WILLIAM K., and WRIGHT, JAMES C. Visualization of a hyperfunctioning parathyroid adenoma using Se^{75} selenomethionine and the photoscanner. *J. Nuclear Med.*, Sept., 1964, 5, 710-714. (From: Department of Internal Medicine and Nuclear Medicine Service. The University of Texas Medical Branch, Galveston, Texas.)

Radioactive isotopes have recently been used to study the parathyroid glands. $\text{Co}^{57}\text{B}_{12}$ and Se^{75} selenomethionine were found to be concentrated in the parathyroid glands. Di Guilio, Sisson and Beierwaltes found that $\text{Co}^{57}\text{B}_{12}$ concentrated 2 to 3 times greater in the parathyroid tissue than in the thyroid, muscle or blood. They located a parathyroid adenoma preoperatively in 1 patient.

The authors report a case of hyperparathyroidism in which a hyperfunctioning parathyroid adenoma was demonstrated near the lower portion of the left lobe of the thyroid gland. A dose of 200 μc of Se^{75} selenomethionine was given and a scan of the neck 2 hours later showed a concentration of radioactivity in the lower left neck in the region of the palpable nodule. A photoscanner was done and there was a marked increase in radioactivity in the region of the nodule. A thyroid scan was then done after a tracer dose of 100 μc of I^{131} , and the scan was normal with no concentration of the I^{131} in the area of the nodule. A 3x2 cm. parathyroid adenoma was removed at operation. Tissue studies showed a five-fold increase in radioactivity concentration in the parathyroid adenoma over that of the thyroid, a three-fold increase over that of the muscle, and a six-fold increase over that of the blood.

The authors have had two additional patients with parathyroid adenomas and a small adenoma was

localized with the scan 4 hours after the injection of 200 μc of Se^{75} selenomethionine. A larger adenoma was not detected in the same patient. The scan was negative in the other patient.

The authors did not use special diets and drugs, and it is possible that they might enhance the test. They believe that further clinical experience using the Se^{75} selenomethionine to demonstrate hyperfunctioning parathyroid adenomas is needed to determine a definite place for this procedure in clinical practice.—*Charles W. Cooley, M.D.*

JANTET, G. H., EDWARDS, J. M., GOUGH, M. H., and KINMONTH, J. B. Endolymphatic therapy with radioactive gold for malignant melanoma. *Brit. M. J.*, Oct 10, 1964, 2, 904-906. (From: St. Mary's Hospital, Paddington, and St. Thomas's Hospital Medical School, London, England.)

Thirteen patients with malignant melanoma were treated by wide excision of the primary tumor followed by direct injection of radioactive colloidal gold into the regional lymph vessels and thus into the regional lymph nodes. Twelve patients had no evidence of distant metastases. Prophylactic lymph node dissections were not done. The basic technique employed for injection of lymph vessels was the same as is used for diagnostic studies. The volume of radioactive colloidal gold (Au^{198}) injected ranged from 0.25 to 2.8 ml. over a 5 minute period. The latter part of the volume was injected to cause more extravasation in lymphatics. Doses ranged from 16 mc to 70 mc, giving a calculated dose of 20,000 rads to 70,000 rads to the lymph nodes. The higher doses were used later in the study.

Follow-up periods ranged from 1.5 to 5 years. None of the 13 patients developed lymph node metastases. Of 8 patients treated with wide excision of the primary melanoma between 1957-1963, 7 have developed lymph node or more distant metastases and 6 have died.

Because of the promising results of the study, the authors believe that a large scale trial on a statistical basis is warranted. Such treatment may offer a satisfactory means of treating Stage I cases of melanoma for which treatment has been most difficult to plan and controversial in nature.—*William K. Littman, M.D.*

HARRIS, C. C., JORDAN, J. C., SATTERFIELD, M. M., GOODRICH, JACK K., STONE, H. L., and HILL, REBECCA. A collimator for scanning with low-energy photons. *J. Nuclear Med.*, Sept., 1964, 5, 653-656. (From: Oak Ridge National Laboratory, Oak Ridge, Tenn., and University of Mississippi Medical Center, Jackson, Miss.)

Collimators furnished with commercially available

scanners were found to be unsatisfactory for scanning experiments using gamma energies in the 30-90 kev. range, or such as those produced by I^{125} , Cs^{131} or Hg^{197} . The counting rates were low and the ability to show small areas of activity was poor. The collimators were designed for the 280-410 kev. range. The septa were not thick enough for the higher energies and were too thick for the lower energies, resulting in low transmission.

The authors needed a collimator for cardiac scanning experiments using Cs^{131} . A collimator was designed and assembled using tapered hexagonal tubes made of lead foil of a thickness of 0.005 inch. This thickness of foil was easy to work with and showed

little leakage at 30 kev. The hexagonal holes gave a 10 per cent greater transmission than the round holes. A total of 109 full tubes and several split tubes was glued together to make a circle to fit the existing shield for the 3-inch diameter crystal. The collimator was unnecessarily long for the I^{125} studies, but was reasonably good with Hg^{197} . The isoresponse curves for Hg^{197} did not differ significantly from those for I^{125} except at the lowest levels.

The authors concluded that this collimator will provide resolution quite comparable to that of a 3 inch 61-hole collimator in the 70 kev. range, and with the advantage that the on-target count rate would be doubled.—*Charles W. Cooley, M.D.*



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